The New England
Journal of Medicine

Copyright, 1949, by the Massachusetts Medical Society

Volume 241 OCTOBER 6, 1949 Number 14

NATIONAL HEALTH SERVICE — RECOMMENDATIONS OF THE HOOVER COMMISSION*

HUGH R. LEAVELL, M.D., DR.P.H.†

BOSTON

FORMATION of the Commission on Organization of the Executive Branch of the Government, more widely known as the Hoover Commission, was authorized by the eightieth Congress. Its duties were to investigate activities of the Executive Branch with the objectives of limiting expenditures as far as possible consistent with proper performance of essential services; doing away with overlapping and duplication; consolidating similar services and abolishing unnecessary ones; and defining the limits of executive function. The President appointed four members of the Commission; four were appointed by the President of the Senate, and four by the Speaker of the House of Representatives. Twenty-three task forces or committees were set up by the Commission to study various federal activities. One of these was the Committee on Medical Services of which the Honorable Tracey S. Voorhees was chairman. The Commission was obviously not obligated to accept all the findings of its task forces. Major recommendations of the Committee on Medical Services, however, were accepted though the Commission itself divided on certain matters, some members presenting their views in minority reports.

Medical and public-health operations of the federal Government during the 1948 fiscal year cost one and a quarter billion dollars. Three major agencies spent most of this money: the Veterans Administration 61 per cent, the armed forces 20 per cent, and the Federal Security Agency 14 per cent. Of the total expenditure, 85 per cent was for direct medical care, 4 per cent for research, and the rest for public-health services, training and administration. Some 24,000,000 Americans are beneficiaries to a greater or less degree of the federal medical care program. Eighteen and a half million veterans make up the largest group and stand in a somewhat middle position between the 3,000,000 members of the armed forces with their dependents, in addition to merchant seamen for whom complete medical care is provided, and the 2,000,000 federal civilian employees receiving only an industrial health service.

Many more weaknesses were found in the medical care program of the federal Government than in public health and research. Some major weaknesses are especially noteworthy: agencies compete with each other for scarce personnel, hospitals are constructed without an over-all plan, and facilities available are not utilized to maximum efficiency. The quality of medical care provided by different agencies varies considerably. Congress has failed to define a clear policy on beneficiaries. The best use of private practitioners and university medical personnel is not made in the medical care program. Preventive medicine and research are not emphasized as they should be if the greatly increasing costs of medical care are to be reduced. Federal assistance needed so much by medical schools and other health-training institutions is lacking.

Since no one person is responsible for the over-all federal health operations, there is competition among agencies for scarce medical and technical personnel. At the time the report was made the Veterans Administration had 5600 beds closed because of insufficient personnel to staff existing facilities. In the armed forces the shortage is particularly acute with the idea general that a draft may be necessary to provide medical personnel, since voluntary recruitment is failing to meet the need. Even with a draft applying only to younger doctors, there would be a shortage of specialists.

Hospitals are being constructed by various federal agencies without relation to the plans or needs of other federal agencies or to those of voluntary, state and local governmental hospitals. Construction costs vary greatly, ranging from $20,000 to as high as $51,000 per bed, with the estimated cost to voluntary hospital construction at the present time about $16,000 per bed. Nearly half the hospitals of the Veterans Administration are planned to be built in areas where experience has shown that staffing would be extremely difficult if not impossible. In a number of medical centers, it was found that various hospitals of the armed forces, the Veterans Administration and the Public Health Service showed definite lack of integration and waste both of plants and of medical personnel because there was no over-

*Presented at the annual meeting of the Massachusetts Medical Society, Worcester, May 24, 1949.

†Professor of public-health practice, Harvard School of Public Health.

all plan for utilization. It was recommended that "hospital care for federal beneficiaries should be planned in relationship to the hospital resources of the country as a whole, not merely through construction of federal hospitals as a class apart."[1] Federal patients requiring hospitalization should be placed in nonfederal hospitals on a reimbursable basis instead of further enlargement of the federal hospital plant. In other words, nonfederal facilities being constructed under the Hill–Burton Act should be co-ordinated with the federal hospital system.

The quality of medical care available to beneficiaries of the federal Government varies greatly depending on which agency provides the service, whether or not facilities operated by this particular agency are readily available, whether sufficient technical personnel is at hand and so forth.

Congress has failed to define clearly its policy regarding beneficiaries of federal medical service. For example, veterans with nonservice-connected disabilities are entitled to hospital care under the vague authorization "if beds are available." As a matter of fact, 100,000 beds have been built to make them available for this group, since Congress has simply not faced the issue squarely. On the other hand, preventive services that might avoid subsequent costly hospitalization cannot be given to veterans without service-connected disability. Care for dependents of Army personnel is based on an authorization sixty years old providing that "whenever practicable" these dependents shall be provided with care. As a matter of fact, some 900,000 dependents of Army personnel are presently considered eligible.

The best possible use has not been made of highly skilled practitioners and personnel available through university medical schools. The Veterans Administration has made an excellent beginning and established a number of hospital programs in conjunction with medical schools, but this is a rather recent development and it certainly is fair to state that in general the objective has been to set up a full-time staff for federal hospitals with relatively little attention to the possibilities of utilizing part-time services from physicians serving the general public.

Major Recommendations

To meet the weaknesses found, a united medical administration is recommended. This would be formed by consolidation of the major activities of the federal Government in medical care, medical research and public health, with an operating division in each of these principal fields. A division of staff services would provide for management, research, control of finance, personnel, supply and so on. Major activities to be included in the united medical administration would be medical care activities of the Veterans Administration, general hospitals and post or station hospitals (except those in isolated areas) of the armed forces within the continental United States, the entire Public Health Service, nonmilitary hospitals in the Canal Zone and the Food and Drug Administration.

The armed forces medical services would retain all responsibility for activities overseas, for military preventive medicine and for outlying post and station hospitals within the continental United States. Each of the forces would also retain a medical center for training and research. Medical care of Indians and federal prisoners would be provided by agencies presently responsible for these services, but united medical administration personnel would be assigned to work in these agencies. The Soldiers' Home, the Naval Home and health functions incidental to the operation of various federal agencies, such as the Atomic Energy Commission and the Tennessee Valley Authority, would not be included.

At the head of the united medical administration would be the ablest health and medical administrator obtainable. He and his top assistants would be appointed by the President and confirmed by the Senate. A career service for technical personnel would be developed on a basis somewhat similar to that now operating successfully for such personnel in the Veterans Administration. An advisory board to assist the administrator would consist of the Surgeons General of the Army and Navy, the Air Surgeon and the Administrator of Veterans Affairs.

Congressional action is necessary to define clearly the beneficiaries entitled to governmental medical care and to prescribe ways in which this care should be made available.

Control of armed forces medical policies should be exercised by the Secretary of Defense. In each geographic area where members of the armed forces and others are operating under military control, responsibility for hospitalization and much of the outpatient care for all United States personnel in the area should be assigned to a single one of the armed forces.

Although there is obviously a need for federal assistance to medical and health education, it is indefinite to the point that a survey is required to determine the exact amount of federal assistance necessary.

"The necessity for medical care which requires heavy expenditures and much personnel, must not be permitted to result in minimizing the even greater importance of controlling disease."[2] Therefore, research, preventive medicine and public health are given the highest priority in the Commission's report. At numerous points in the report the idea is stressed that only by knowledge and application of new methods of controlling disease can the increasing costs of medical care be reduced.

Independent Health Agency

The Committee on Medical Services at first worked on the assumption that the Hoover Commission would recommend a combined department

of health, education and security. Later the Commission indicated that such a recommendation might not be made and asked the Committee what its reaction would be to an independent health agency. The suggestion was that such a plan might be preferable to the combined department. The Commission, in its final report, was divided on the question. It was pointed out that in a combined agency, co-ordination of health, education and security would obviously be simpler than in separate departments. The combined agency would meet the Commission's objectives of reducing the number of agencies reporting to the President to a manageable number. The tendency for overemphasis on professionalism would be reduced to a minimum in the combined organization. It was suggested by one member of the Commission that even if a separate agency were established for medical care, the public-health functions should be part of a combined department so that health activities relating primarily to state and local governments could be co-ordinated with similar programs operated by the federal Government in the fields of health, education and welfare. This type of arrangement, however, would separate curative and preventive health activities of the federal Government and would therefore be undesirable.

In an independent agency, health functions would be segregated and not subject to irrelevant considerations relating to education and welfare. This might be desirable for certain other departments such as the armed forces, which would use medical services only. Health appropriations could be identified clearly as such. The implementation of special personnel policies considered necessary for the health field might be easier in a separate agency than if health were only one bureau of a combined department. In the separate agency pay and status of the top personnel would doubtless be higher and therefore more attractive than those of a bureau chief and his major subordinates in a combined department. It was suggested that even though a combination might eventually be desirable, the problem of integrating all the medical services to be included in the united health administration was such a great one that even if only as an initial step, a separate agency would be desirable.

Value of Preventive Medicine

At many points in its report the Commission and the Committee on Medical Services stressed the importance of preventive medicine. All phases of the health program must receive proper emphasis if the best results are to be obtained. Medical care programs and medical research carried on by the federal Government must be related intimately to activities in public health and preventive medicine. As new procedures are made available by research they must be incorporated promptly into practice. The public must be told what is available and induced to obtain for themselves the benefits of modern medical science. In this way members of the health team concerned with diagnosis and treatment of disease should be relieved of an increasing part of their heavy burden. With the passage of time it may be that people will more and more come to regard disease as a result of failure to apply available knowledge rather than as the result of bad luck.

At the moment it is extremely difficult to estimate with any accuracy possible savings in the cost of illness that could be accomplished through full use of all present knowledge of disease prevention. Health and productivity are intangible values, and it is unprofitable to attempt complete separation of prevention and treatment, since one merges imperceptibly into the other. Incomplete statistics of illness rates also complicate the problem. Some direct costs of illness may be computed fairly satisfactorily, such as doctors' bills, medicines and hospitalization, in addition to wages lost because of illness and potential earning power lost through premature death. However, it is difficult to compute the cost to industry of idle machines and impairment of productivity of other workers by absence of the sick man.

As of 1948, expenditures for medical care were estimated at $8,000,000,000 per year, and the loss in output due to disease and injury estimated at $27,000,000,000 annually. How much of this amount could be saved if all known preventive measures were applied to the fullest possible extent and if research were supported at the optimum level to make new methods of prevention, health promotion, medical care and rehabilitation available as rapidly as possible? Of course, no one can answer this question. However, the results would undoubtedly be astounding. A few examples of what may be accomplished by preventive measures will give some indication of the results that might be expected:

Industry — Employers report that a first class medical and safety department will reduce occupational disease 63 per cent, absenteeism 30 per cent, compensation cost 29 per cent and labor turnover by 27 per cent.

Armed Forces — Various types of vaccination, plus sanitation and D.D.T. made losses due to typhoid fever, smallpox, typhus, cholera, plague, yellow fever and tetanus negligible. Malaria was a minor problem within the U. S. and responded satisfactorily to vigorous control measures in the Pacific. Through x-ray screening at induction centers 150,000 cases of tuberculosis were kept out of the armed forces, and the tuberculosis incidence among the forces and among veterans since the war has been only about one tenth that of World War I. Deaths from disease were a much smaller proportion of total deaths than in any previous war, with a 1:16 disease to battle death ratio in World War II; an approximately equal ratio in World War I and a 13:1 ratio in the Spanish War.

Cancer — If all the 334,000 new cancer cases each year had the best modern treatment in stages possible with early diagnosis we might anticipate about 200,000 five-year cures contrasted with about 9000 from the average type of treatment given after cancer becomes widespread.

Tuberculosis — Based on 1943 standards the annual cost of tuberculosis to the nation is estimated at 356 million dollars. If we were willing to spend only 31 million more each year for ten years, it is estimated that tuberculosis

could be so reduced that only 37 million a year would be needed thereafter to keep it under control.

Malaria — The estimated 2 million cases a year cost some 500 million dollars. Based on control programs around military areas during World War II, it is stated that with 53 millions spent over seven years malaria could be virtually eradicated so that only a quarter million a year would be needed thereafter to keep it under control.

Maternal and Child Health — If the entire country had the infant mortality and maternal mortality rates of our best states, nearly 22,000 infants and 2100 mothers would be saved annually.

Life Expectation — At birth, life expectation for white females is now 70.3 years having increased steadily by over 25 years since 1890 due largely to control of communicable diseases and better infant care. However, expectation at age 50 is increasing only slowly because diseases of later life have not yet been greatly affected by preventive measures. Based on experience of other countries, it is not at all unreasonable to hope for three or four additional years expectation at 50.

If the 15 major causes of death during the productive period from 20-65 were completely eliminated, 178,500,000 years of productive life would be added for white males alone and life expectancy at 20 increased by 3.95 years. Some of the most important causes of death during this period are definitely amenable to preventive measures now available. A reasonably conservative estimate indicates that of the theoretically possible addition of 3.95 years, 1.95 could be achieved by full application of our present knowledge.

Summary

These are but a few examples of what preventive medicine can accomplish. Implementation of the Hoover Commission recommendations would provide a unified service giving proper emphasis to research and preventive medicine as well as to medical care.

References

1. Committee on Medical Services, Commission on Organization, Executive Branch of Government. *Medical Activities: Report to Congress.* 57 pp. Washington, D.C.: U. S. Government Printing Office, 1949. P. 17.
2. *Ibid.* P. 30.

PROCAINE PENICILLIN G FOR AQUEOUS INJECTION*

A Study of Blood and Urine Levels

Major Edwin J. Pulaski, M.C., U.S.A.,† and Captain James F. Connell, Jr., M.C., A.U.S.‡

FT. SAM HOUSTON, TEXAS

RECENT developments in penicillin-therapy dosage schedules have resulted in numerous studies dealing with the significance of blood levels. The object of this communication is to report data concerning the blood plasma penicillin levels and urine concentration curves following intramuscular administration of aqueous solution of procaine penicillin (Crysticillin).§

This procaine salt is relatively insoluble in aqueous solutions and body fluids, and this property forms the basis of a new principle in penicillin administration. It has been demonstrated that the addition of dried sodium carboxymethylcellulose to dry crystalline procaine penicillin G results in a stable suspension in diluents containing water. Sodium carboxymethylcellulose forms a viscous gel, which maintains

Table 1. *Levels of Crysticillin Assayed in Blood Serum and Urine after One Injection of 4000 Units per Kilogram of Body Weight.*

Hours After Injection	Level							Range	
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7		
	unit/cc.	unit/cc.	unit/cc.	unit/cc.	unit/cc.	unit/cc.	unit/cc.	unit/cc.	
Serum:									
1	0.6	0.3	0.62	0.31	2.5	1.25	2.5	0.31 -	2.5
3	0.6	0.6	1.25	0.31	0.62	0.31	1.25	0.31 -	1.25
6	0.6	0.6	0.62	0.31	0.31	0.31	0.62	0.31 -	0.62
12	0.0175	0.3	0.04	0.16	0.16	0.16	0.31	0.04 -	0.31
18	—	0.08	—	0.16	0.08	0.08	0.04	0.04 -	0.46
24	—	0.04	—	0.08	0.04	0.04	0.04	0.04 -	0.08
36	—	—	—	0.04	0.04	—	—	—	—
48	—	—	—	—	0.04	—	—	—	—
Urine:									
3	200.0	200.0	321.0	72.0	240.0	220.0	230.0	72.0 -	200.0
6	200.0	200.0	225.0	160.0	210.0	230.0	220.0	160.0 -	200.0
12	200.0	120.0	50.0	120.0	200.0	166.0	210.0	50.0 -	200.0
18	*	200.0	19.5	23.0	100.0	133.0	166.0	19.5 -	200.0
24	76.0	21.0	0.6	50.0	*	45.0	2.1	0.6 -	76.0
30	20.0	21.0	0.6	23.0	*	19.0	1.6	0.6 -	230.0
36	0.4	1.6	0.05	21.0	23.0	2.1	1.0	0.4 -	23.0
48	—	0.05	—	3.4	1.6	0.8	0.8	0.4 -	3.4
54	—	—	—	0.1	*	—	—	—	—
60	—	—	—	0.04	—	0.8	0.8	—	—
72	—	—	—	—	—	0.8	0.8	—	—

*No specimen.

*From the Surgical Research Unit, Brooke General Hospital, Brooke Army Medical Center.

†Assistant professor of clinical surgery, Baylor University School of Medicine; chief of septic surgery and chief, Surgical Research Unit, Brooke General Hospital, Brooke Army Medical Center.

‡Research associate, Surgical Research Unit, Brooke General Hospital, Brooke Army Medical Center.

§The Crysticillin used in this study was kindly supplied by Dr. Charles H. Mann, of E. R. Squibb and Sons, New York City.

the procaine penicillin in discrete particulate suspension. This has eliminated the necessity for the use of oils.

A number of investigators have made a survey of this preparation, including Whittlesey and Hewitt,[1] Robinson et al.[2] and Stollerman and his associates.[3]

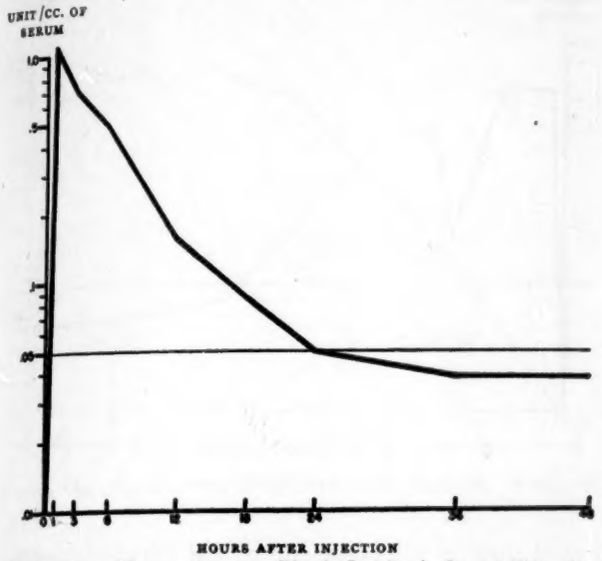

FIGURE 1. *Mean Average Blood Level of Crysticillin in 7 Patients.*

According to Whittlesey and Hewitt, all subjects receiving an injection of 300,000 units showed demonstrable levels after twelve hours, and assayable levels were still demonstrable in three quarters of the patients after twenty-four hours. With a single injection of 600,000 units all subjects showed demonstrable levels at twenty-four hours. Our study is essentially a confirmation and extension of these findings.

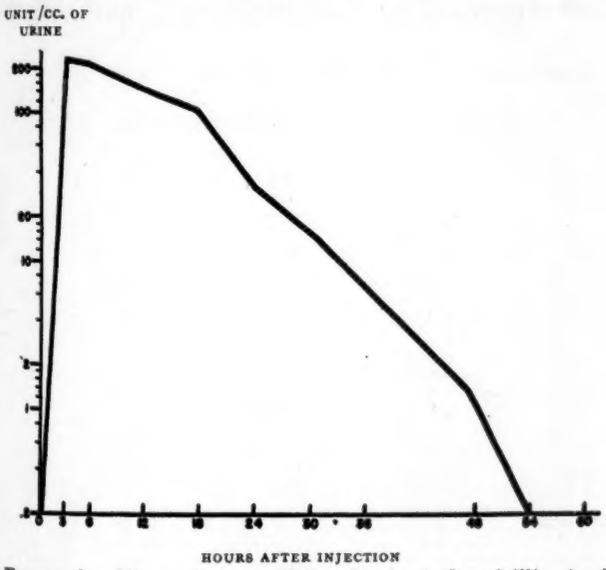

FIGURE 2. *Mean Average Urine Level of Crysticillin in 7 Patients.*

MATERIALS AND METHODS

Procaine penicillin G (Crysticillin) is prepared for use by suspension of the powder in sterile distilled water or sterile isotonic solutions of sodium chloride. This suspension has been administered to young male adults in one, two or three injections on a basic dosage of 4000 units per kilogram of body weight. This approximates 1 cc. per dose of 300,000 units per cubic centimeter of material.

TABLE 2. *Levels of Crysticillin Assayed in Blood Serum and Urine after Two Injections Eight Hours Apart.*

Hours After Injection	Level				Range	
	Case 1	Case 2	Case 3	Case 4		
	unit/cc.	unit/cc.	unit/cc.	unit/cc.	unit/cc.	
Serum (first injection):						
1	0.63	0.3	0.16	0.16	0.16 -	0.63
3	1.25	0.3	0.3	0.16	0.16 -	1.25
6	0.63	0.3	0.16	0.08	0.08 -	0.63
Serum (second injection):						
8	0.63	0.16	0.16	0.08	0.08 -	0.63
9	1.25	0.3	0.3	0.3	0.3 -	1.25
11	0.63	0.08	0.3	0.3	0.08 -	0.63
14	0.63	0.16	0.3	0.3	0.16 -	0.63
20	0.3	0.16	0.16	0.16	0.16 -	0.3
26	0.16	0.08	0.08	0.16	0.08 -	0.16
32	*	0.02	0.02	0.16	0.02 -	0.16
44	*	—	—	0.08	0.02 -	0.08
Urine (first injection):						
3	333.0	416.0	219.5	225.0	219.5 -	416.0
6	375.0	*	100.0	242.0	100.0 -	375.0
Urine (second injection):						
8	250.0	374.0	200.0	233.0	200.0 -	374.0
11	291.0	416.0	250.0	217.0	217.0 -	416.0
14	375.0	291.0	374.0	225.0	225.0 -	375.0
20	333.0	291.0	291.0	225.0	225.0 -	333.0
26	225.0	250.0	333.0	150.0	150.0 -	333.0
32	100.0	70.0	250.0	125.0	70.0 -	250.0
44	7.8	60.0	225.0	*	7.8 -	225.0
50	3.4	14.6	90.0	7.2	3.4 -	90.0
60	12.0	*	60.0	*	12.0 -	60.0

*No specimen.

Blood serum was assayed for penicillin by the Rammelkamp[4] method using a strain of beta-hemolytic streptococci sensitive to 0.004 units per cubic centimeter of penicillin. The paper-disk plate method[5] was employed to determine the level of

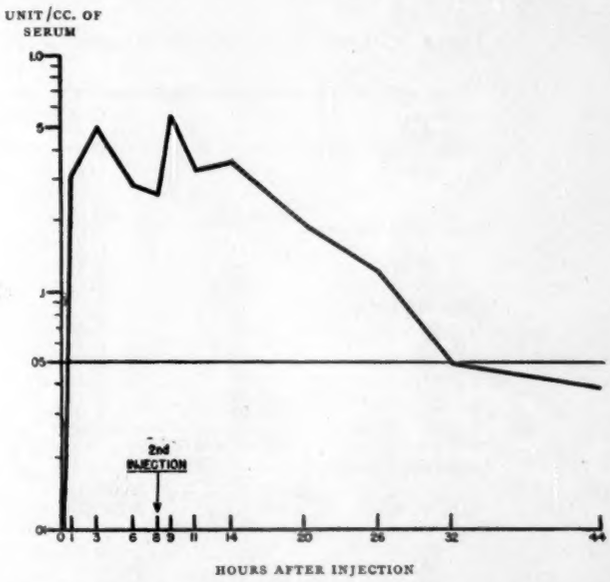

FIGURE 3. *Average Blood Level of Crysticillin in 4 Patients Fifty Hours after the First and Forty-Two Hours after the Second Injection.*

penicillin in urine. A strain of hemolytic staphylococci sensitive to 0.06 units per cubic centimeter of penicillin was the test organism.

Results

A series of 7 patients received one intramuscular injection of 4000 units of aqueous procaine penicillin per kilogram of body weight (Table 1).

The blood levels obtained show that a peak level of 0.3-2.5 units per cubic centimeter of serum is achieved between the first and third hours after injection. This was approximately halved six hours after injection, and assayable levels were present at eighteen hours in 4 of the 5 specimens tested. Urine samples collected from these patients at the time that blood was drawn contained levels of penicillin in excess of 50 units per cubic centimeter for twelve hours after the penicillin injection. The fluid intake was not restricted in any patient. The urine contained penicillin for thirty-six hours after the injected dose in all cases and at the forty-eight-hour period in a few.

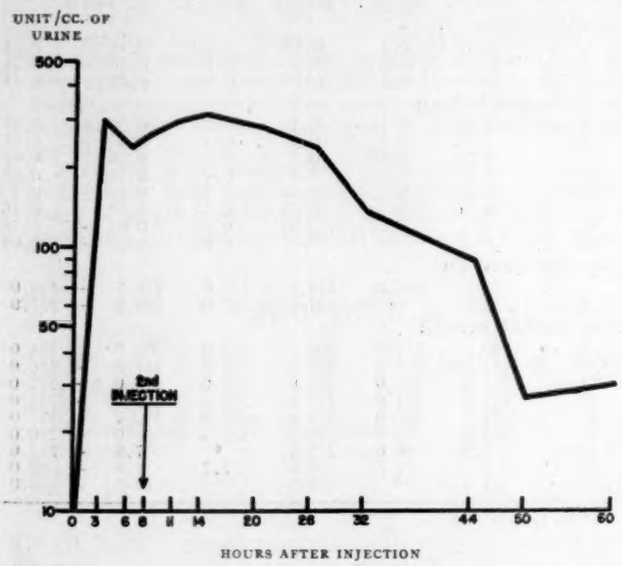

FIGURE 4. *Average Urine Level of Crysticillin in 4 Patients Fifty Hours after the First and Forty-Two Hours after the Second Injection.*

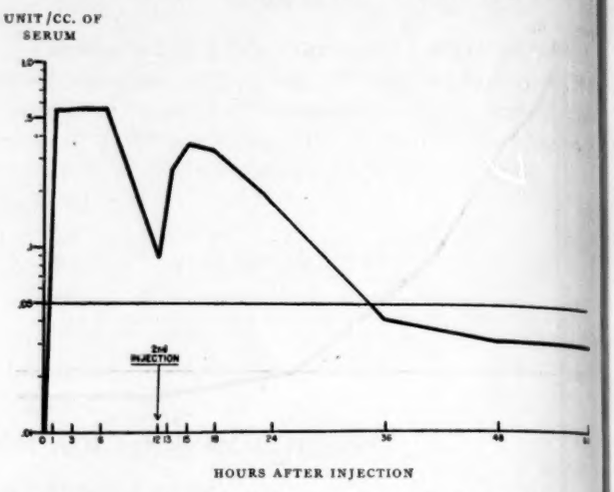

FIGURE 5. *Average Blood Level of Crysticillin after the Second Injection.*

The mean average blood and urine levels obtained in this series of 7 patients are presented graphically in Figure 1 and 2. On this basis, it appears that significant penicillin levels are obtained in the blood for at least eighteen hours and in the urine for at least thirty-six hours after injection.

A series of 4 patients were given a second injection of 4000 units of aqueous procaine penicillin per kilogram of body weight eight hours after the first injection. Results as shown (Table 2) reveal that

TABLE 3. *Levels of Crysticillin Assayed in Blood Serum and Urine after Two Injections Twelve Hours Apart.*

Hours After Injection	Level				Range	
	Case 1	Case 2	Case 3	Case 4		
	units/cc.	*units/cc.*	*units/cc.*	*units/cc.*	*units/cc.*	
Serum (first injection):						
1	0.14	0.6	1.2	0.31	0.14 -	1.2
3	0.14	1.2	0.6	0.31	0.14 -	1.2
6	0.14	1.2	0.6	0.31	0.14 -	1.2
Serum (second injection):						
12	0.07	0.07	0.07	0.16	0.07 -	0.16
13	0.14	0.14	0.56	0.31	0.14 -	0.56
15	0.56	0.14	0.56	0.31	0.14 -	0.56
18	0.56	0.28	0.28	0.31	0.28 -	0.56
24	0.14	0.14	0 14	0.31	0.14 -	0.31
36	<0.0175	0.035	<0.0175	0.08	<0.0175 -	0.08
48	—	<0.0175	—	<0.04	—	—
60	<0.0175	—	—	—	—	—
Urine (first injection):						
3	>200.0	>200.0	>200.0	72.0	72.0 -	>200.0
6	200.0	>200.0	>200.0	89.0	89.0 -	>200.0
Urine (second injection):						
12	92.0	>200.0	>200.0	72.0	72.0 -	>200.0
15	>200.0	>200.0	*	78.0	78.0 -	>200.0
18	100.0	>200.0	*	78.0	78.0 -	>200.0
24	17.5	96.0	400.0	160.0	17.5 -	400.0
36	96.0	84.0	166.0	50.0	50.0 -	166.0
42	7.9	68.0	*	*	7.9 -	68.0
48	1.1	*	25.0	23.0	1.1 -	25.0
60	<.4	*	5.8	<0.4	<0.04 -	5.8
72	—	*	<0.4	—	—	—

*No specimen.

assayable serum levels are present eighteen hours after the second injection and twenty-six hours after the first injection in all patients. Assayable urine levels are present fifty hours after the first and forty-two hours after the second injection of 4000 units. The average blood serum and urine levels are illustrated in Figure 3 and 4.

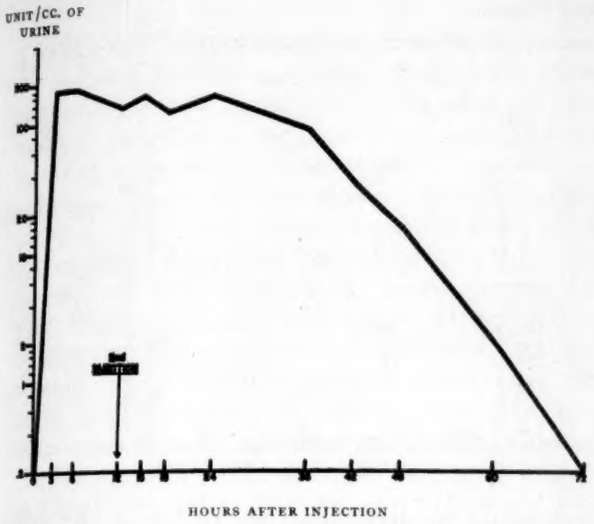

FIGURE 6. *Average Urine Level of Crysticillin after the Second Injection.*

Another series of 4 patients received a second injection of 4000 units of aqueous procaine penicillin per kilogram of body weight twelve hours after the first injection. The results (Table 3) indicate blood levels in all patients twenty-four hours after the first and twelve hours after the second injection; 2 of the 4 patients had assayable blood levels eighteen hours after the second injection (Fig. 5). In all patients, assayable levels in the urine were present at least thirty-six hours after the second injection (Fig. 6).

Blood serum and urine assays also were determined in a series of patients receiving large single doses of Crysticillin, as follows: 10,000 units per kilogram of body weight in 5 patients (Table 4); 12,000 units in 4 patients (Table 5); and 16,000 units in 5 patients (Table 6 and Fig. 7 and 8). All patients had blood serum levels after more than thirty-six hours. Urine levels in excess of 10 units per cubic centimeter were found in all patients thirty-six hours after injection, and assayable levels in excess of 1 unit were present in most cases at forty-eight hours.

No local or systemic reactions occurred in any of the patients during or after the administration of the drug.

TABLE 5. *Levels of Crysticillin Assayed in Serum and Urine after One Injection of 12,000 Units per Kilogram of Body Weight.*

Hours After Injection	Level				Range
	Case 1	Case 2	Case 3	Case 4	
Serum:	*unit/cc.*	*unit/cc.*	*unit/cc.*	*unit/cc.*	*unit/cc.*
1	1.15	1.2	6.1	4.0	1.15 - 6.1
3	1.4	3.5	5.5	3.25	1.4 - 5.5
6	0.7	1.4	5.5	2.75	0.7 - 5.5
12	0.4	1.0	1.87	1.92	0.4 - 1.92
24	0.3	0.16	0.34	0.4	0.16 - 0.4
36	0.2	0.2	0.19	0.4	0.19 - 0.4
48	—	0.16	0.16	0.16	— - 0.16
Urine:					
3	160.0	190.0	190.0	205.0	160.0 - 205.0
6	140.0	200.0	180.0	150.0	140.0 - 200.0
12	125.0	178.0	160.0	130.0	125.0 - 178.0
24	130.0	68.0	100.0	70.0	68.0 - 130.0
30	105.0	11.3	47.5	20.3	11.3 - 105.0
36	100.0	0.8	6.25	0.8	0.8 - 100.0
48	80.0	—	0.96	—	0.96 - 80.0

TABLE 4. *Levels of Crysticillin Assayed in Serum and Urine after One Injection of 10,000 Units per Kilogram of Body Weight.*

Hours After Injection	Level					Range
	Case 1	Case 2	Case 3	Case 4	Case 5	
Serum:	*unit/cc.*	*unit/cc.*	*unit/cc.*	*unit/cc.*	*unit/cc.*	*unit/cc.*
1	6.7	2.4	1.15	1.15	0.9	0.9 - 6.7
3	5.0	3.2	1.60	1.70	1.25	1.25 - 5.0
6	5.0	1.5	2.50	1.60	1.60	1.5 - 5.0
12	1.0	0.6	0.9	0.9	0.93	0.6 - 1.0
24	0.8	0.2	0.24	0.62	0.2	0.2 - 0.8
36	0.2	0.3	0.3	0.06	0.03	0.03 - 0.3
48	0.3	—	0.04	—	—	0.04 - 0.3
Urine:						
3	180.0	210.0	180.0	180.0	140.0	140.0 - 210.0
6	61.1	140.0	200.0	180.0	200.0	61.1 - 200.0
12	72.2	120.0	160.0	200.0	160.0	72.2 - 200.0
24	2.1	100.0	120.0	25.0	50.0	2.1 - 120.0
36	0.96	25.0	100.0	1.0	37.0	0.96 - 100.0
48	0.20	0.8	21.0	0.8	0.09	0.09 - 21.0

Summary

Three dosage schedules of aqueous procaine penicillin were studied in three groups of patients comprising young adult males. With a dosage of 4000 units per kilogram of body weight, assayable levels were detected in the blood and urine at least eighteen hours and thirty-six hours, respectively, after intramuscular injection. In each case when the dose was repeated eight hours later assayable blood levels were present twenty-six hours and assayable urine levels fifty hours after the first injection. In patients receiving the same initial dose at intervals of twelve hours blood levels were present in all patients twenty-four hours after the first injection and in 2 of the 4 patients thirty-six hours after the first injection. The urine still contained penicillin forty-eight hours after the first injection. Single doses of 10,000, 12,000 and 16,000 units of aqueous procaine penicillin per kilogram of body weight were administered intramuscularly to three groups of patients. In all patients assayable blood levels could be determined for thirty-six and urine levels for forty-eight hours.

TABLE 6. *Levels of Crysticillin Assayed in Serum and Urine after One Injection of 16,000 Units per Kilogram of Body Weight.*

Hours After Injection	Level					Range
	Case 1	Case 2	Case 3	Case 4	Case 5	
Serum:	unit/cc.	unit/cc.	unit/cc.	unit/cc.	unit/cc.	unit/cc.
1	4.06	1.1	3.75	2.75	2.5	1.1 - 4.06
3	4.37	3.5	4.5	4.0	3.3	3.3 - 4.5
6	5.0	1.4	3.87	1.6	1.6	1.4 - 5.0
12	3.75	1.0	2.5	0.7	0.9	0.7 - 3.75
24	0.62	0.16	0.7	0.16	0.3	0.16 - 0.7
36	0.19	0.19	0.16	0.3	—	0.16 - 0.3
48	—	0.16	—	—	—	— 0.16
Urine:						
3	170.0	190.0	250.0	145.0	145.0	145.0 - 250.0
6	195.0	200.0	165.0	130.0	125.0	125.0 - 200.0
12	150.0	178.0	150.0	125.0	110.0	110.0 - 178.0
24	100.0	68.0	125.0	25.0	30.0	30.0 - 125.0
30	82.0	11.3	110.0	0.8	2.9	0.8 - 82.0
36	32.5	0.8	70.0	—	0.8	0.8 - 70.0
48	0.96	—	5.9	—	—	0.96 - 5.9

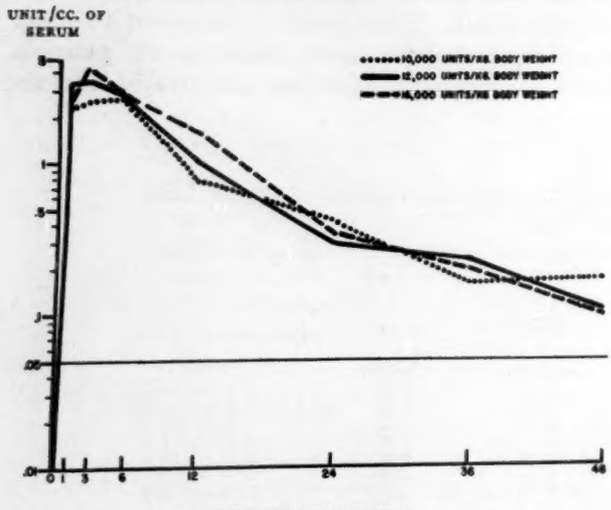

FIGURE 7. *Average Blood Level of Crysticillin after Various Doses of the Drug.*

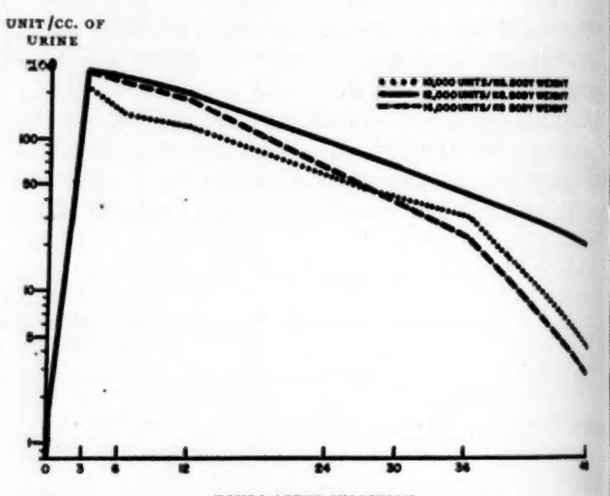

FIGURE 8. *Average Urine Level of Crysticillin after Various Doses of the Drug.*

We are grateful for the technical assistance of Barbara A. Parrish, S.B., and Ruth Latta, A.B.

References

1. Whittlesey, P., and Hewitt, W. L. Serum concentrations of penicillin following administration of crystalline procaine penicillin G in aqueous suspension. *Proc. Soc. Exper. Biol. & Med.* **68**:658-661, 1948.
2. Robinson, J. A., Hirsh, H. L., Milloff, B., and Dowling, H. F. Procaine penicillin: therapeutic efficiency and comparative study of absorption of suspensions in oil and in oil plus aluminum monostearate and of aqueous suspension containing sodium carboxymethylcellulose. *J. Lab. & Clin. Med.* **33**:1232-1240, 1948.
3. Stollerman, G. H., Roston, E. H., and Toharsky, B. Guide to use of procaine penicillin in hospital practice. *New York State J. Med.* **48**:2501-2505, 1948.
4. Rammelkamp, C. H. Method for determining concentration of penicillin in body fluids and exudates. *Proc. Soc. Exper. Biol. & Med.* **51**:95-97, 1942.
5. Loo, Y. H., et al. Assay of streptomycin by paper-disc plate method. *J. Bact.* **50**:701-709, 1945.

THE USE OF PSYCHOTHERAPY IN GENERAL PRACTICE*

LEO ALEXANDER, M.D.†

BOSTON

PSYCHOTHERAPY is part of medical practice. As with any useful medical procedure it should not remain limited to the specialist's office. Like all medical procedures, psychotherapy contains elements of art as well as of science.

In the practice of psychotherapy actions and attitudes are frequently more important than words. Emotionally sick adult people have a good deal in common with children, in particular the fact that their complaints and abnormal actions frequently express their feelings and problems in a symbolic rather than a direct manner, that they both frequently distrust words, that they learn more from example and the opportunity to identify themselves with good leadership than from precept, and that they relate themselves to the world more through emotional experience than according to instruction. Thus, how the doctor acts toward the patient, how he listens to him and how he speaks to him is often more important than what he tells the patient. It is frequently of greater value to offer new good interpersonal experiences than new thought content, although both are inextricably interwoven.

In its most elemental and nonverbal form, psychotherapy can be carried out successfully even on animals.[1, 2] It is obvious that in the treatment of animals attitudes and actions play the main part, since animals do not understand words. But the ability to influence animals or human beings by attitudes and actions is the most important natural gift of the psychotherapist.

If I were asked to devise a screening test by which candidates gifted for psychotherapeutic work could be discovered, I should say that the person most likely to become a good psychotherapist was the type of person to whom stray dogs take easily, who could effectively gain the confidence of beaten dogs or who could easily ride an anxious horse that was sensitive to the bit and that customarily shied at the slightest provocation. I should place much more emphasis upon these faculties and attitudes, which are inherent as well as acquired, than upon theoretic psychodynamic knowledge. The psychotherapist must constantly keep in mind that his actions and his attitudes are at least as important as his words.

Once the principle has been understood the technics can be learned. They fall essentially into the following groups: supportive treatment; ventilation; shift of emphasis; interpretation; and reassurance. It is of particular importance, of course, to know the limits of these various forms of psychotherapy and to know when to add other methods such as medicinal forms of treatment or when to refer patients to a specialist for more intensive abreactive or interpretive psychotherapy or for the various forms of shock treatment, such as electric shock or insulin coma treatment[3] to modify successfully abnormal emotional or mental states.

MAIN PSYCHOTHERAPEUTIC TECHNICS

Supportive Treatment

The main element of supportive treatment is the doctor's attitude. Irrespective of whether the patient comes to him with a physical ailment or with a neuropsychiatric disease manifested by physical complaints, it is of fundamental importance that the doctor listen to the complaint, take it seriously and subject the patient to a thorough physical examination. The thoroughness of an examination frequently determines the success of supportive treatment. The effect of such treatment is, of course, enhanced by the doctor's reputation in the community — by his standing as a professional man and citizen. Both a doctor's reputation and his thoroughness enhance each other; conversely, it can sometimes be disastrous if a well qualified and highly respected physician takes the complaint of the patient lightly and because of his initial impression and shortage of time subjects him to a hurried and superficial examination. This can increase the feeling of rejection at the hands of life, which may be the main factor in the neurosis of an unsuccessful man or a rejected, unloved woman or child. The doctor must give, by his attitude and actions, the assurance to the patient that he cares for him, that he is interested in him and that he is eager to help him. There is an old saying that "a specialist is a man who does a rectal examination." I should like to paraphrase this and say that a psychotherapist is a physician who takes a complete and thorough history and who does a complete and thorough physical examination.

The degree to which such an attitude is psychotherapeutic was recently brought home to me by a patient who consulted me in a state of severe anxiety. This forty-six-year-old man complained of extreme nervousness, sweating, pains throughout all bones of his body and attacks of weakness lasting several days at a time. He was very anxious and tense,

*Presented at the annual meeting of the Massachusetts Medical Society, May 26, 1949.

†Instructor in psychiatry, Tufts College Medical School; director, Neurobiologic Unit, Division of Psychiatric Research, Boston State Hospital.

and he was sweating profusely. He sat with his arms tightly pressed to his body. On the examining table his muscles seemed to be in a state of tension, and he had difficulty in relaxing them. He showed a markedly increased startle-pattern response, whereas all spontaneous motor activity was greatly reduced. It may be that I subjected this man to a particularly thorough neurologic examination because I wanted to be sure to find or rule out the existence of an organic neurologic condition, since he had suffered a blast injury, but the inadvertent psychotherapeutic effect of this detailed and painstaking examination was both surprising and delightful. As the examination progressed the patient gradually relaxed, and after it was over he was not only at ease but also cheerful and smiling. He departed in a state of apparent well-being. Without any direct psychotherapy, the acute anxiety state, obviously caused by the fear of having been seriously injured, melted under the impact of a thorough, sympathetic, careful examination, which was terminated by an encouragingly worded verdict of the finding of physical well-being. If this verdict had been rendered after a less painstaking examination, it might very well have aroused resentment and antagonism, followed by a build-up of anxiety and further discouragement. In other acute situational anxiety reactions, regardless of whether they express themselves in fear of injury by a serious accident or a fear of heart disease or any other physical ailment, the verdict of physical health will be acceptable to the patients only if they have been subjected to an examination that they accept as being of sufficient thoroughness, and the doctor must express by his attitude the fact that he has an open mind and that he is interested in finding out the truth.

Part of psychotherapy is teaching, and the most effective way of teaching is by example. If the physician wishes the patient to have an open mind and accept the truth, the patient must first be shown that the physician has an open mind and is interested in the truth himself. In a good relation the patient will unconsciously imitate the physician's own attitude. The arousal of mimesis is indeed the most important instrument of successful teaching, as well as of successful psychotherapy.

Of course, such reassurance cannot overcome a severe, deeply ingrained anxiety neurosis or a prepsychotic panic, but an attitude of a wide-open mind and thoroughness will be helpful even in those conditions, although it may be then wise to withhold reassurance and interpretation until the patient himself is ready to accept them. Again, it is important to know one's limits. Unless the physician is very sure that the patient is ready to accept reassurance and interpretation, both of which must be used with great caution, it is much better to help the patient to stumble upon the solution by merely helping him with an attitude of thoroughness, open-mindedness and interest in the true state of his health. It is important to realize that reassurance is not always real support. The anxious patient who believes that he is dangerously sick will more frequently regard reassurance as a brush-off and a lack of real interest on the part of the physician.

I once treated a young woman with a severe phobic state that had many features of an early schizophrenic psychosis with obsessive features. Nevertheless there was a great deal of meaningful material that prompted me to go on with psychotherapy. This patient had been to many doctors, including psychiatrists, and had left them all after a few visits. After a long course of treatment with many ups and downs, she finally became well fifteen months later. I then asked her, as I frequently do of recovered patients, what in her opinion was the most decisive therapeutic act to which she ascribed her recovery. Her answer was as follows:

> When I went to you for the first time I did not like you, and I almost did not want to come back. When I came the second time I asked you a question — namely, whether I was actually out of my mind. (I had the fear that I was going crazy or had actually gone crazy.) When I asked you that you said, "I don't know. We have to find out first and then do the right thing about it." That gave me confidence in you. All the other doctors I had been to told me that I wasn't out of my mind and that I wasn't going to lose my mind, and I thought that they didn't understand me or they didn't tell me the truth. When you told me that you didn't know, I knew that I could have confidence in you, that you were honest and that you would always tell me the truth. From then on I kept coming back and I got well.

The answer I gave this patient had actually been the truth. After a number of interviews and equivocal tests I was not quite sure whether this was not an acute schizophrenic development that would be better treated with shock or insulin. The weight of evidence finally was in favor of a condition considered modifiable by psychotherapy, which turned out to be effective after some time. I knew it was the ring of truth in my statement that carried the weight. It is essential to realize that emotionally sick people, like children, have an uncanny sense of truth. This is particularly important in dealing with children. The ability of children to look through and size up their parents and others close to them is frequently equal to that of trained psychologists and psychiatrists. True supportive therapy can therefore never be given without the solid foundation of conviction of truth in what the therapist is saying. In supportive treatment one must definitely show that one is on the side of the patient in his battle with the world.

Ventilation

Next in importance to the supportive attitude is that of giving the patients the full opportunity and the setting of understanding approval in which they can freely ventilate their stresses and emotions. Once the patient is started in successful ventila-

tion, the physician should interrupt the patient as little as possible, but merely sit there with the understanding and encouraging smile of the statue of a wise Buddha. This technic is particularly helpful in certain cases of anxiety hysteria as well as in the anxiety states of the older age groups, especially those with hypertension. A good example of the former type is the case of a young married woman, aged thirty-five years, who came to my office in a state of marked distress and agitation, complaining of severe and persistent pain in her left cheek. She held her hand pressed against her cheek, stating that as soon as she released the pressure of her hand the pulsating became unbearable. This constant, throbbing pain had been present for three years. She had consulted a good many doctors, including two neurosurgeons and several dentists, about her complaint. Two weeks before referral to me, the patient went back to her first dentist, who took out an additional tooth (several had previously been extracted), which brought about no improvement. She was then referred to an otolaryngologist for investigation of her ears, nose and throat. He found no physical abnormalities that could be causing her complaint, and referred her for neuropsychiatric examination. She stated that this pain might be due to "something terrible" she had done in early life and that she had a guilty conscience that "bangs in the back of my mind." She then began to tell the grim history of her life. In the psychotherapeutic discussions with this patient I completely refrained from giving any interpretation, but instead merely helped her by occasional questioning to find the meaning of her symptoms herself. After the sixth interview her pain was gone, and recurred later only on two occasions for brief and meaningful periods after the twelfth interview. It remained absent after the thirteenth interview and did not recur at any time within three years of the sixteenth and final psychotherapeutic session.

An equally striking reaction to purely ventilative treatment occurred in a forty-six-year-old man who suffered from a chronic anxiety state with mild hypertension and symptomatic alcoholism. He had previously been refused insurance because of hypertension. When I first examined him, his blood pressure was 175 systolic, 80 diastolic. His wife had been on the verge of leaving him because of his drinking. Psychotherapy in this patient remained entirely ventilative in character. It appeared that he derived particular benefit from the opportunity to "blow off steam" regarding his resentment against his employers and business associates. There was remarkable gradual diminution of his anxiety as well as his hypertension. After three months of treatment his anxiety became sufficiently diminished that he felt able, without, of course, any implication of advice on my part, to take a step that he had wanted to take for many years but had never quite dared to — namely, to resign from his organization and to go into business for himself. Subsequently, his blood-pressure readings remained consistently normal, 130 systolic, 65 diastolic. His symptomatic indulgence in alcoholic beverages likewise improved, and he remained well and congenial with his family.

It is frequently observed that when ventilation proceeds on a purely intellectual level, without associated emotional expression, the therapeutic benefit is minimal or absent. The patients may tell their story, and at the end they may say, "This is my story, Doctor, but what does telling it do for me? I still feel the same way." It is then that one must bring about real emotional participation, an emotional reliving of the stress situation, for which the word abreaction has come into vogue, which literally means to react off or to "blow off steam."

I believe that the physiologic result of abreaction as a form of excitation can best be understood in Pavlovian terms. It is conceivable that the intense excitation of neurons associated with electric shock may be the extreme physical variant of the same principle. It appears that the bringing about of excitation, quite apart from the interpretation and working out of the emotional material, has in itself a wholesome effect, irrespective of whether the excitation was produced by the reliving of a recent crushing-threatening episode, by the bringing out of old resentments by verbalization, by reliving of emotional conflict, by the participation in exciting ritual or by the touching off of extreme excitation of the entire nervous system by an electric stimulus.

It must not be forgotten, however, that in spite of the strong physiologic components of the experience, the reliving and working out and the psychotherapeutic guidance and other forms of psychotherapy and understanding are of the greatest value. In spite of all the lip service given to the unity of mind and body, many physicians find it difficult to accept the fact that there is no separation of the psychologic and the physical aspects of treatments. Both should be utilized to the fullest for the recovery of the patient.

The more specifically psychotherapeutic technics consist of those which promote insight and which have to do with interpretation either directly or indirectly. The indirect method is preferable particularly for the beginner and in the beginning of psychotherapy. It is very important not to overwhelm the patient with interpretation and thereby to build up his defenses and resistances, but it is essential to feel out the patient before attempting to do so. It must be remembered that the scaling of strong defenses is a risky task, in psychotherapy as well as in war. The wise general or the wise psychotherapist will prefer a flanking movement; in the long run it will save time and risk.

Shift of Emphasis

The "flanking movement" that should precede direct interpretation and frequently is sufficient to take the place of direct interpretation is the shift of emphasis. By this I mean the subtle shifting of emphasis from the complaint or the apparent conflict to the more important material that the patient may have presented quite inadvertently without having been consciously aware of its import in relation to his complaint. The advantage of this technic is that it does not arouse antagonism and resistance. It is wise to take as a starting point something that the patient himself has told one.

A recent example is afforded by the case of a fifty-year-old man who reported to the outpatient clinic with a complaint of severe pain throughout the left side of the chest, for which he had first consulted the heart clinic, which referred him for neuropsychiatric consultation for the differential diagnosis of intercostal neuralgia or psychoneurosis. As frequently happens, the patient gave his problem away with the first sentence he spoke when he introduced himself. He said, "I want to explain to you why I come to this out-patient clinic instead of consulting a private doctor. I am a pharmacist, but I can't work in my line here in Massachusetts because my degree is not recognized here; but my wife wants us to live here because of our son. Therefore I have to work as a storeroom clerk and can hardly make enough money to get by." He then described with great vividness the pains in the left side of his chest. He felt deeply distressed and alarmed about them, and they were a very profound reality to him. Careful examination in addition to the clinical and laboratory tests done before convinced me that this patient was not suffering from organic disease. Furthermore, his marked state of anxiety and depression was positive evidence of an emotionally determined illness. On the other hand I believed that he would not take well to direct interpretation. At the conclusion of the examination, which I had carried out with great thoroughness, I imperceptibly shifted from the discussion of his complaints to that of his life situation. Very soon the patient was well in the process of discussing his impasse and obviously eager for what suggestions would be made. I dropped the hint that many illnesses improve provided the patient is happy or finds a way of being happy. Before long we were discussing ways of improving his life situation. It turned out that a compromise was feasible. A neighboring state was chosen where he could work in his own field and yet be sufficiently near his son to suit his wife. The mere possibility of doing something about his problem and the support implied in the assumption that he had a right to consider his own occupational happiness relieved him. In the course of readjustment of his life situation the pain vanished, and the danger of antagonizing the patient by the direct proffering of insight was avoided.

Interpretation

Although I refer here to interpretation of emotional illness, I believe it also holds true for physical illness that interpretation of the illness to the patient is an important part of medical management of the sick person. Interpretation is the most difficult part of psychotherapy; it requires the greatest amount of skill, tact and timing. It should not be attempted until one is very sure of one's ground and after one has established a good relation with the patient. The results are seldom as dramatic as those portrayed in the motion pictures. It is rather a slow process of understanding, and results from a continued co-operative effort of doctor and patient. Nevertheless, there are occasional cases in which a dramatic denouement may be achieved by a well timed interpretation for which the patient is ready. The most important thing is to interpret in terms acceptable to the patient. A genuine understanding of the patient is a prerequisite for such a procedure to be carried out successfully.

Even in insight-promoting treatment, actions and attitudes are an important instrument of therapy. The actions and attitudes that have been found beneficial and helpful on the basis of psychodynamic understanding are remarkably similar, even identical, with those derived from true religious attitudes. F. Alexander and M. T. French[4] pointed out that the priest in Victor Hugo's novel *Les Miserables*, written as long ago as 1862, reformed the hero of the story, Jean Valjean, who had tried to rob him, by treating him with attitudes and acts of unexpected kindness, which constituted a masterpiece of brief psychotherapy. It is of fundamental importance that age-old spiritual insight and modern psychodynamic insight have led to the same conclusion: that certain thieves are deprived people who must first be given to before they can be reformed. It is likewise of interest in this connection that modern psychotherapy has rediscovered the value of love, in the spiritual sense of the word, as a therapeutic force.

Like all therapy that offers or suggests insight, even actions and attitudes if they serve that end are resisted by defenses to which the patient will cling until he becomes free enough to give them up. Thus, Jean Valjean's first reaction to the priest's kindness was one of a temporary recrudescence of his hostile behavior before he became able to give it up altogether. F. Alexander and French point out that even in this respect Valjean's reform conformed to the familiar rebounding pattern of response of a symptom or neurotic attitude to psychotherapy. This pattern also conforms to Pavlov's laws of the higher nervous activity of the cortex: in Pavlovian terms this initial negative reaction could be described as negative induction by a new

conditioned stimulus followed by positive induction that reinforces the stimulus sufficiently to allow it to irradiate. It appears that psychotherapy is a real force conforming to spiritual as well as to natural laws.

Reassurance

It is essential for reassurance that the patient believe that the doctor is truthful and that he has been sufficiently thorough to know whereof he speaks. In actual mental illnesses or severe neuroses, reassurance is of only secondary importance apart from its use as an adjunct to general supportive technic. Reassurance, however, is of great importance as a preventive measure. Irrespective of whether or not a physician chooses to treat overt neuropsychiatric conditions in his practice, there is one field in which he must do psychotherapy — that is, whenever he deals with chronic or incurable physical illnesses. In these conditions a great deal depends on the doctor's psychotherapeutic handling of the problem. The existence of such an illness constitutes severe neurosis-producing stress, and this superimposed neurosis or depression frequently makes the difference between an invalid and a reasonably active and well adjusted person. The way in which the physician handles such a problem may prevent, control or, on the other hand, sometimes even precipitate the superimposed neurosis. Thorough, warm understanding of the patient with a knowledge of his emotional needs will do a great deal to prevent superimposed neurosis in such cases. The problem begins with the way in which the diagnosis should be told to the patient. I personally favor giving the patient the true diagnosis, but in encouraging terms. Not telling the diagnosis sometimes makes the patients fear a worse possibility than even that which the well meaning physician has withheld. Another important point is to maintain in the patient a feeling of control — a feeling that he can do something for himself. Abandonment to fate constitutes extreme stress that few people, not even some of the most sturdy combat personnel in war, can take.

One should therefore never tell the patient "There is nothing I can do for you," without at least offering a program of things that he could do for himself and continuing to show a helpful interest. All too frequently such patients are abandoned to their own devices. The rationalization for doing so is usually a perfectly ethical one. The real motive, however, is more complicated. The chronically or incurably ill patient represents a tremendous challenge to the physician's opinion of his own healing abilities, which will frequently put him on the defensive, especially when the patient on his part enhances this challenge by openly hostile, demanding or critical attitudes. It is therefore understandable that in such a setting the doctor, especially when he is sensitive to criticism and hostility, may tell the patient that he can do nothing for him in such a way as to imply "There is nothing anybody can do for you," which to the patient means complete rejection and abandonment. It must never be forgotten that a principal function of the physician is to give hope to the patient and to relieve his relatives of responsibility by not dodging any responsibility himself.

It is also important to guard against an attitude of rejection in referring mental patients to a psychiatrist. The manner of the referral frequently determines success or failure of the patient's first contact with the psychiatrist and conditions his readiness to accept treatment. If the physician refers the patient with an attitude of rejection and detached disinterestedness in his problem, which to the patient implies "You are crazy, and you ought to go to a psychiatrist," he will go to the psychiatrist with a chip on his shoulder and co-operation will be difficult to obtain. If, however, the physician refers the patient to the psychiatrist in the same manner in which he would refer a patient to any other specialist, saying, for instance, "I want you to see my friend Dr. so and so; he is a specialist in this field, I am sure he will help you and I shall keep in close touch with him," the patient and his relatives will come prepared to have confidence and co-operation will result as a matter of course in a smooth and automatic manner.

Conclusion

I should like to conclude this paper with a few do's and don't's in the use of psychotherapy in office practice. In general one cannot go wrong with a warm supporting attitude, and in offering the patient opportunity for ventilation. If this ventilation should be associated with a marked emotional abreaction, the objective, supporting attitude must be maintained in the face of it, even if this abreaction should include the expression of hostility toward the physician. One should not interpret unless one is really sure of the ground — much damage can be done by novices.

If the patient improves only at the price of too much dependence on the therapist, or if he becomes dependent without improving, he should be referred to a person with more skill and experience in the field of psychiatry. It should be remembered that dependence is regression into an infantile state. Although the regression is sometimes necessary as a transitory phase during treatment, and frequently is undesirable even then, one must ultimately wean the patient and help him to mature. A physician of my acquaintance who rather prides himself on his self-taught skill in his psychotherapeutic management of neurotic patients told me once as a proof of his accomplishments that his cured neurotic patients retained so much confidence in him that for

years after treatment they would make no major decision without asking his advice, even in entirely nonmedical matters. To me this sounded as if a surgeon were taking pride in the fact that his patients were letting him dress their still-draining incisions for years after each operation. The primary goal must be kept firmly in mind: to help patients to achieve health, happiness, maturity and independence. In every psychotherapy there comes the time when one must throw the ball of responsibility determinedly to the patient, and trust him to carry it.

433 Marlborough Street

References

1. Pavlov, I. P. *Lectures on Conditioned Reflexes.* Translated by W. H. Grant. 2 vol. London: Lawrence & Wishart. Vol. 1, 1928. 414 pp. Vol. 2, 1941. 199 pp.
2. Konorski, J. *Conditioned Reflexes and Neuron Organization.* 267 pp. Cambridge: University Press, 1948.
3. Sargant, W., and Slater, E. *Introduction to the Physical Methods of Treatment in Psychiatry.* 180 pp. Edinburgh: E. & S. Livingstone, 1944.
4. Alexander, F., and French, M. T. *Psychoanalytic Therapy: Principles and application.* 353 pp. New York: Ronald Press Company, 1946.

SYPHILITIC AORTITIS WITH OBSTRUCTION OF MULTIPLE AORTIC OSTIA*

Wiley F. Barker, M.D.†

BOSTON

UNTREATED or inadequately treated late syphilis is no longer so frequently seen by the average physician, and its exotic complications are becoming curiosities. The following case presents one of the more unusual cardiovascular complications.

Case Report

S. L. (P.B.B.H. 7A850), a 52-year-old shipping clerk, was admitted to the Peter Bent Brigham Hospital on March 15, 1948, complaining of severe pain in the anterior part of the chest radiating down the left arm. This symptom had been present, especially on exertion, for about 10 months. The initial episode of pain had occurred while he was walking one evening; a sense of constriction in the chest and a pain in the left arm developed. After resting for several minutes he had been able to return home. Other attacks following a similar pattern became more severe and more frequent. Four months before admission he was admitted to another hospital for diagnostic studies.

Physical examination had revealed a markedly apprehensive man. There was a barely palpable radial pulse on the right; the left radial pulse was weak but palpable. The right carotid pulse was scarcely palpable, but the left carotid pulsation was full and bounding. There was no evidence of cardiac enlargement or other cardiovascular defect.

A positive serologic test for syphilis was obtained. Other blood examinations were within normal limits. An electrocardiogram was interpreted as showing myocardial changes, with a rate of 72 and nodal rhythm. The PR interval was 0.09 to 0.12 second, and the QRS complex was normal. RT was depressed in Lead 1, V_4 and V_5. The P waves were inverted in Lead 2 and 3 and upright in Lead 4. The T waves were diphasic in Lead 1 and V_5, upright in Lead 2 and 3 and low in Lead V_4.

The patient was discharged to the care of his physician with a diagnosis of anxiety state, angina pectoris, syphilis and a suspected congenital anomaly of the great vessels. Six million units of penicillin in oil was administered at home over the course of 10 days. There was no Jarisch–Herxheimer reaction and no subsequent reversal of the blood Hinton reaction to negative.

Symptoms continued, and the patient was given various medications including opiates, salicylates, Demerol, chloral hydrate and barbiturates without significant relief from pain. Nitroglycerin afforded only brief palliation. The severity and frequency of the attacks progressed until 4 days before admission, when the pain and sense of constriction became unremitting, with continued reference of pain down the arm, unrelieved by nitroglycerin. He had had no marked dyspnea, orthopnea, ankle edema or cyanosis, but he had complained of profuse sweating and a sense of impending disaster. He was referred to this hospital by his physician.

Further past history was limited by the patient's inability to answer all questions. He had had no other significant illnesses and no operations. He denied any venereal disease other than gonococcal urethritis as a young man. He stated that as far back as he could remember he had had a small pulse in his left arm and an almost impalpable pulse in his right arm.

The patient was apprehensive and ashen faced, sweating profusely, and complaining of pain in the chest and left arm. The pupils were normal. No abnormalities of the nervous system were demonstrable. The chest was clear on the left, but on the right there was basal dullness, with diminution of breath sounds, bronchial breathing and moist rales. The right carotid pulsation was absent; a moderate pulsation was present in the left carotid. No pulse could be detected in the radial vessels on either side. Femoral and dorsalis-pedis pulses were palpable but weak. The heart was not enlarged; the sounds were normal and without murmurs or friction rub. The abdomen was slightly distended, without fluid, and the liver edge was palpable but nontender three fingerbreadths below the costal margin. There was no abdominal tenderness.

The temperature was 101.8°F. (by rectum), the pulse 104, and the respirations 30. The blood pressure was 0 in the arms and 100 systolic in the legs as determined by palpation of the dorsalis pedis.

Films of the chest taken at the bedside revealed a high diaphragm and a fairly marked degree of pulmonary congestion and edema. The heart appeared slightly enlarged to the right and to the left, although the right border could not be seen in its entirety. The aorta did not appear widened.

The urine was acid, with a specific gravity of 1.033. No albumin was found, but there was a + test for sugar and acetone. Rare red and white cells and hyaline casts were reported in the spun sediment. The hemoglobin was 15 gm. per 100 cc., and the hematocrit 44 per cent. The corrected sedimentation rate was 21 mm. per hour (normal, 15 mm.). The white-cell count was 19,650, with 68 per cent neutrophils, 17 per cent band forms, 11 per cent lymphocytes and 4 per cent monocytes.

Electrocardiograms revealed an abnormal form of ventricular complex — the ST segment was depressed in Lead 1 and markedly depressed in Lead 2 and 3; the T wave was inverted in Lead 3. The unipolar limb leads showed an elevated ST segment, late inversion of the T wave in Lead AVR, elevated ST segment in Lead V_1 to V_3 and depressed ST segment in Lead V_4 to V_6. These tracings were considered suggestive of infarction of the anterolateral aspect of the left ventricle, with subendocardial extension.

Three hours after admission the heart suddenly stopped, with continuation of respiratory movements for a few cycles. The diagnoses were coronary thrombosis with myocardial infarction, syphilis with suspected aortitis involving the coronary ostia, congenital anomaly of the aorta and possible dissecting aneurysm.

*From the Department of Pathology, Peter Bent Brigham Hospital.
†Graduate assistant in pathology, Peter Bent Brigham Hospital.

At post-mortem examination, performed 3 hours after death, the body was that of a well developed and well nourished man. There was no peripheral edema. The abdominal cavity contained no free fluid. The liver weighed 2080 gm. and was severely congested. The remainder of the gastrointestinal and genitourinary systems was normal.

There was bilateral hydrothorax, with 500 cc. of clear, straw-colored fluid in the right pleural cavity and 350 cc. in the left. There was no undue fluid in the pericardial cavity.

The heart weighed 380 gm. and was not enlarged. The pericardium was normal. The right ventricular myocardium measured 0.3 cm., and the left ventricular myocardium 1.4 cm. in thickness. There was a narrow layer of subendocardial infarction measuring 0.3 cm. in thickness encircling the entire left ventricular cavity, with maximal changes anteriorly at a point midway between the base and the apex. The auricles were grossly normal. There was no evidence of valvular disease. The aortic ring showed no dilatation and no separation at the commissures. The measurements were as follows: tricuspid valve, 12 cm.; pulmonary valve, 7.5 cm.; mitral valve, 11 cm.; and auriculoventricular valve, 6 cm.

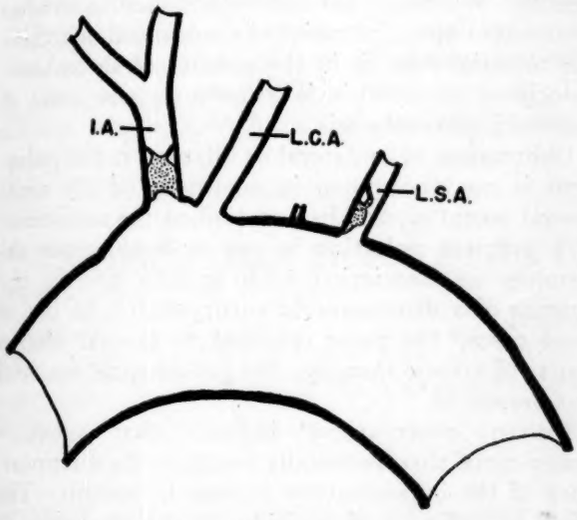

FIGURE 1. *Longitudinal Section of the Aortic Arch and Its Branches, Showing Syphilitic Endarteritis.*

The coronary arteries were patent throughout their course in the myocardium; at their ostia, however, there was marked thickening of the intima, which had almost obliterated the coronary orifice. At no other point in the course of the main coronary vessels and their main branches was there encroachment upon the lumen, although several small, yellowish atheromatous plaques were seen. The anatomic distribution and the origin of the arteries were normal.

The aorta arose from the heart in the usual manner and pursued a normal course throughout the chest. At the arch the innominate artery and the right common carotid artery arose in close proximity from the apex of a small, shallow outpouching of the superior surface of the arch, which measured 3.5 by 2.5 cm. and was 0.7 cm. in depth. The left subclavian artery arose from its normal position. Innumerable yellow plaques of atheroma were present from the level of the innominate artery down to the renal arteries. Most of these plaques were slightly elevated but intact; a few, however, were ulcerated. Between the atheromatous plaques in the ascending and descending aorta there was longitudinal wrinkling of the intima in a characteristic "tree-bark" pattern. The wall of the aorta was thickened except for the small outpouching described above and for a small disk-shaped area, 0.8 cm. in diameter, in the mid-thoracic aorta, where there was marked thinning. It was believed that the origin of the common carotid artery from the apex of the small aneurysmal pouch constituted an anomalous placement of this vessel.

The proximal portion of the lumen of the innominate artery was completely occluded by a smooth, adherent, pinkish-gray tissue. This occluding mass began about 0.5 cm. from the orifice of the vessel and extended along its course for 1 cm. The distal surface of this obstruction was composed of two leaf-like cusps with a concavity directed distally (Fig. 1). Distal to this obstruction the vessel was patent, and bifurcated within 2 cm. into normal common carotid and subclavian arteries, which followed normal paths into the root of the neck.

The orifice of the left common carotid artery was normal except for its displacement to the right, and for the fact that it was dilated, measuring 1 cm. in diameter. It crossed the mediastinum and ascended into the neck in a normal position.

The left subclavian artery was markedly narrowed near its orifice by a valve-like piece of pinkish-gray tissue, similar to that obstructing the innominate artery, leaving a lumen less than 0.3 cm. in diameter. The distal course and distribution of the left subclavian were normal. The superior and inferior thyroid arteries were greatly dilated and tortuous, measuring 0.3 cm. in diameter.

The lungs showed some basal congestion.

The principal microscopical findings of interest were limited to the heart and great vessels. The changes in the heart were confined to the inner fourth of the wall of the left ventricle and were seen maximally in the interventricular septum, anterior left ventricle and lateral left ventricular wall. In this region there was an ischemic necrosis of the muscle fibers. There was disappearance and fragmentation of the nuclei in this zone. Minimal numbers of polymorphonuclear, lymphocytic and monocytic cells were seen between the fibers. This was interpreted as a myocardial infarction of less than 4 days' duration. The remaining myocardium showed an irregularly

FIGURE 2. *Section of the Innominate Artery, Showing Obliteration of the Lumen by the Intimal Proliferation and the Destruction of the Media (Elastic-Tissue Stain).*

scattered fibrosis, and many of the small arteries showed a hyaline intimal thickening encroaching upon the lumen.

The narrowing observed at the coronary ostia was due to a hyaline fibrous tissue containing an occasional lipoid-laden macrophage. There were many focal infiltrations with round cells. Some of these were found in the vessel walls near the junction of media and intima; the most marked infiltration was in the adventitia around the vasa vasorum. Sections taken through the site of obstruction in the innominate and subclavian vessels demonstrated a similar hyaline thickening of the intima, with focal infiltrations of round cells. The media of the innominate artery showed marked destruction and replacement with a vascular fibrous tissue (Fig. 2 and 3);

FIGURE 3. *Section of the Innominate Artery, Showing the Destructive Process in the Media under Higher Power (Elastic-Tissue Stain).*

similar, less marked changes were seen in the elastic tissue of the subclavian artery and the coronary arteries near their orifices.

Multiple sections through the aortic wall showed similar changes; focal infiltrations with round cells, especially around the vasa vasorum; marked intimal proliferation due to a hyaline fibrous tissue; and patchy irregular destruction of the elastic tissue of the media and replacement with a vascular fibrous tissue. There was intimal proliferation in the vasa vasorum. Small atheromatous pools were occasionally seen but contributed little to the over-all picture.

Levaditi's silver stains on all tissue blocks failed to reveal any recognizable spirochetes.

The final pathological diagnoses were as follows: syphilitic aortitis, with aneurysm of the terminal portion of the ascending aorta; syphilitic endarteritis involving the right and left coronary orifices and the orifices of the innominate artery and the left subclavian artery; subendocardial infarction of the left ventricle; cardiac failure as evidenced by passive congestion of the liver and abdominal viscera, and by bilateral hydrothorax; and anomalous origin of the left common carotid artery.

DISCUSSION

Stenosis of the coronary ostia with subsequent myocardial infarction is well described in the literature.[1-5] Involvement of the coronary arteries in their course in the myocardium and involvement of other arteries of medium and smaller size is well known. The classic pathological picture is primarily an endarteritis of the vasa vasorum in the adventitia, with a secondary but nonsyphilitic intimal proliferation in response. There is also a marked destructive process involving the elastic tissue in the larger vessels, with replacement by fibrous elements.

In spite of the common pathological picture, there is difficulty in making the clinical diagnosis of ostial stenosis. Woodruff[6] has cited this difficulty and has commented upon the rarity of myocardial infarction due to ostial stenosis in the absence of thrombosis. Associated thrombosis is usually on the basis of unrelated atheromatosis.

Obliteration of unilateral or bilateral radial pulsations is not uncommon in aneurysm of the arch; several recent reports have described the occurrence of a deficient pulsation in one or both upper extremities in association with syphilis and in the absence of a demonstrable aneurysm.[7, 8] In one of these cases,[8] the pulse returned to normal after a course of arsenic therapy. No pathological material was presented.

Current observations[9] indicate that adequate heavy-metal therapy usually results in the disappearance of the inflammatory process in aortitis. The place and efficacy of penicillin in the treatment of late cardiovascular syphilis is as yet undefined.[10, 11] Certainly 6,000,000 units of penicillin administered in the case reported above did not remove the evidences of active inflammatory processes although no recognizable spirochetes were to be found. It is perhaps confirmatory of the concepts of Moritz,[1] Saphir[2] and Warthin[3] that there was no regression of the secondary intimal proliferation, which was the actual obstructing agent in these vessels.

The electrocardiographic findings immediately prior to death were strongly suggestive of the total deficiency of the coronary supply as opposed to the solely focal changes more common in the usual atherosclerotic thrombosis. This case is being presented elsewhere as part of a series with electrocardiographic demonstration of subendocardial ischemia.[12]

In retrospect, then, it is possible to reach a diagnosis on the basis of the positive serologic test for syphilis, the unremitting angina and subsequent myocardial infarction, the aberrations of the pulses and the electrocardiograms suggesting "global ischemia." There is no satisfactory explanation of the patient's statement that he had always had deficient radial pulses. The pathological picture was clearly that of a syphilitic process and not that

of a congenital defect; the presumptive explanation is that the obliteration of the great vessels had occurred early in the course of the disease when the patient was still a young man.

Summary

A case of syphilitic aortitis and endarteritis in which there was obliteration of the lumen of the innominate artery, partial obstruction to the lumen of the left subclavian artery and almost complete occlusion of the coronary ostia is reported. The patient pursued a steadily downhill course to die of myocardial infarction without actual coronary thrombosis, ten months after the onset of symptoms, and in spite of antisyphilitic therapy with penicillin.

The diagnosis of coronary-ostia disease should be more readily suspected when, in association with electrocardiographic changes of "global ischemia," there is evidence of other ostial obstruction, with or without a demonstrable aortic aneurysm. The current relative infrequency of late cardiovascular manifestations of syphilis renders them nonetheless important.

References

1. Moritz, A. R. Syphilitic coronary arteritis. *Arch. Path.* **11**:44-59, 1931.
2. Saphir, O. Involvement of medium-sized arteries associated with syphilitic aortitis. *Am. J. Path.* 5:397-406, 1929.
3. Warthin, A. S. Syphilis of medium and smaller arteries. *New York M. J.* **115**:69-73, 1922.
4. Jones, E., and Bedford, D. E. Syphilitic angina pectoris. *Brit. Heart J.* 5:107-120, 1943.
5. Fuller, R. H., and Ryder, H. W. Heart disease secondary to syphilitic aortitis. *Ohio State M. J.* **39**:1126-1128, 1943.
6. Woodruff, J. O. Cardiovascular syphilis. *Am. J. Med.* **4**:248-278, 1948.
7. Casiello, A., and Hanono, M. Ausencia de pulso en miembros superiores y carótida derecha en una aortópatia luética. *Rev. méd. de Rosario* **34**:1159-1162, 1944.
8. Pijoan de Beristain, C. Desaparición del pulso radial en la aortitis sifilitica simple. *Semana méd. espan.* 6:178, 1943.
9. Webster, B., and Reader, G. R. Effect of antisyphilitic treatment on microscopic appearance of syphilitic aortitis. *Am. J. Syph., Gonorr. & Ven. Dis.* **32**:19-27, 1948.
10. Reynolds, F. W. Treatment failures following use of penicillin in late syphilis. *Am. J. Syph., Gonorr. & Ven. Dis.* **32**:233-242, 1948.
11. Tucker, H. A., and Farmer, T. W. Penicillin in cardiovascular syphilis: early reactions to administration. *Arch. Int. Med.* **80**:322-327, 1947.
12. Levine, H. D., and Ford, R. V. Unpublished data.

PUNCH LIVER BIOPSY IN THE DIAGNOSIS OF MILIARY TUBERCULOSIS

Report of a Case

CHARLES G. CRADDOCK, M.D.,* AND H. C. MEREDITH, JR., M.D.†

CHARLOTTESVILLE, VIRGINIA

SINCE it is often difficult to substantiate a suspected diagnosis of miliary tuberculosis, an additional practical diagnostic procedure would be of value. As it is well known that miliary tubercles are scattered throughout the liver in this disease,[1-3] histologic study of a specimen of liver tissue would be of unquestioned value in confirming a clinical impression. In recent years punch liver biopsy has been established as a simple, practical and safe method of obtaining a specimen of liver tissue satisfactory for microscopical study and causes very little discomfort to the patient.[4-8] Liver biopsy is not generally recognized as a method for the diagnosis of miliary tuberculosis, and since references to its use in the literature are scanty,[4, 5, 9] it is the purpose of this paper to offer the procedure as a practical method for diagnosing the disease.

The technic of punch liver biopsy using either the subcostal or the intercostal approach has been ably reported by Hoffbauer,[6] Volwiler and Jones,[5] Popper et al.,[8] Topp and his co-workers[10] and others.[7] The Roth–Turkel[11] and the Silverman[12] biopsy needles are those in most common use and yield quite satisfactory specimens for histologic examination. This material can also be used for culturing.[9] The mortality of the procedure is extremely low if the usual precautions are taken, Topp et al.[10] having recently reported a series of 350 liver biopsies without serious complications or mortality.

The following case, recently observed at the University of Virginia Hospital, illustrates the diagnostic value of this procedure in substantiating a suspected diagnosis of miliary tuberculosis.

Case Report

A 26-year-old Negro had been well until 5 weeks before admission, when he first had a severe pleuritic pain in the right side of the chest. This was associated with a hacking cough, chills, fever, drenching sweats, anorexia and weight loss. A few days later he was admitted to another hospital, where he went progressively downhill and became critically ill and semistuporous. The temperature varied between 101 and 104°F. An x-ray film of the chest was reported as suggestive of miliary tuberculosis but was considered more consistent with a fungous infection. Penicillin, sulfonamides, aureomycin and a few doses of streptomycin were tried without effect, and the patient was transferred to the University of Virginia Hospital on March 15, 1949 for further studies.

Physical examination revealed an emaciated patient who appeared acutely ill. The other significant findings were in the chest. There was splinting of the right side of the thorax, with slight to moderate dullness up to the fourth and fifth ribs anteriorly. A few bubbling rales could be heard in the right base, and in the region of the right apex there were a few crepitant rales.

The temperature was 102°F., the pulse 95, and the respirations 25. The blood pressure was 110/70.

*Assistant resident, Department of Internal Medicine, University of Virginia Hospital.

†Resident, Department of Internal Medicine, University of Virginia Hospital.

Examination of the blood showed a red-cell count of 4,300,000, with a hemoglobin of 13 gm., and a white-cell count of 5000, with 74 per cent neutrophils. Repeated blood cultures were negative. No acid-fast bacilli were found on several examinations of the sputum, gastric washings and direct bone-marrow smears. Specimens from each of these were also cultured for tubercle bacilli. Tuberculin and histoplasmin skin tests were negative, as were studies of the urine, stool and spinal fluid. Bone-marrow examination showed nothing pathognomonic, but there was an increase in plasma cells of 5 to 10 per cent.

X-ray films of the chest showed both lung fields to be involved with a miliary type of nodulation. When the examination was repeated 2 days later areas of miliary density were again seen scattered throughout both lung fields but were thought to be more suggestive of a fungous disease than of typical miliary tuberculosis.

The temperature ranged between 101 and 105°F., and the patient continued to look critically ill. Dihydrostreptomycin was started on the 3rd hospital day, since it was believed that the patient probably had miliary tuberculosis.

A punch liver biopsy was done on the 4th hospital day by the intercostal route, and the histopathological report* was as follows:

> Throughout this liver tissue are many small lesions that are rather typical small tubercles. The center of the lesions contains some necrotic material; around the margins of the lesions epithelioid cells, numerous lymphocytes and an occasional giant cell can be seen. Special staining technics for acid-fast bacilli reveal the presence of a few acid bacilli in these tubercles.

The diagnosis was miliary tuberculosis of the liver.

After the biopsy report the dosage of streptomycin was increased to 3 gm. daily, and promizole was begun in a dosage of 1 gm. every 6 hours. On the 6th day of streptomycin therapy the temperature started gradually down. The appetite began to improve and soon became enormous, the patient often consuming six large meals a day. Three blood transfusions were given to correct an anemia that had developed. At the end of the 4th week of hospitalization the bone-marrow culture was reported positive for tubercle bacilli. The patient continued to improve and to gain weight and was discharged to a sanatorium.

Discussion

As illustrated in this case, liver biopsy may offer a practical method for confirming a diagnosis of miliary tuberculosis when other methods fail. The diagnosis was strongly suspected in this patient but the chest x-ray films were equivocal and the usual measures for immediate bacteriologic substantiation were unsuccessful. Even though streptomycin had been started in this case, punch biopsy was able to establish the diagnosis.

It should be emphasized that preliminary cultures and sputum examinations should first be carried out intensively. It is our opinion that if the diagnosis of miliary tuberculosis is strongly suspected but cannot be immediately confirmed, streptomycin therapy should be started and liver biopsy considered for early confirmation of the diagnosis. A conclusive diagnosis early in the course of the disease would be helpful since one could then concentrate all effort on the proper treatment of the tuberculosis without subjecting the patient to other diagnostic tests and therapeutic trials in an attempt to eliminate other diagnoses. The initiation of streptomycin therapy before or after performance of the liver biopsy should minimize the risk of further spreading of the disease. It seems, however, illogical to place much emphasis on the hazard of further complicating the disease in this way, since widespread hematogenous diffusion of the bacteria to practically all organs has already occurred.

With the correct diagnosis of miliary tuberculosis quickly and easily established by punch liver biopsy, treatment can be instituted with less delay, and a better prognosis can thus be made possible.

*We are indebted to the Pathology Department, University of Virginia Hospital, for the histopathological interpretations of the biopsy specimens.

Summary

Punch liver biopsy is offered as a relatively simple, safe and practical method for the diagnosis of miliary tuberculosis when other procedures fail. A case is presented to illustrate its value.

References

1. Boyd, W. *The Pathology of Internal Disease.* Fourth edition. 857 pp. Philadelphia: Lea & Febiger, 1944. P. 327.
2. *Idem. A Textbook of Pathology.* Fourth edition. 1008 pp. Philadelphia: Lea & Febiger, 1943. P. 535.
3. Bell, E. T. *A Textbook of Pathology.* Fifth edition. 862 pp. Philadelphia: Lea & Febiger, 1944. P. 550.
4. Gillman, T. and Gillman, J. Modified liver aspiration biopsy apparatus and technique, with special reference to its clinical applications as assessed by 500 biopsies. *South African J. M. Sc.* **10**:53-66, 1945.
5. Volwiler, W., and Jones, C. M. Diagnostic and therapeutic value of liver biopsies: with particular reference to trocar biopsy. *New Eng. J. Med.* **237**:651-656, 1947.
6. Hoffbauer, F. W. Needle biopsy of liver. *J. A. M. A.* **134**:666-670, 1947.
7. Davis, W. D., Scott, R. W., and Lund, Z. Needle biopsy of liver. *Am. J. M. Sc.* **212**:449-461, 1946.
8. Popper, H., Steigmann, F., Meyer, K. A., Kozoll, D. D., and Franklin, M. Correlation of liver function and liver structure: clinical applications. *Am. J. Med.* **6**:278-291, 1949.
9. Wocdruff, C. E., Kelly, R. G., and Leaming, M. A. Culturing of tubercle bacilli from human spleen, liver and kidney. *Am. Rev. Tuberc.* **48**:76-81, 1943.
10. Topp, J. H., Linder, M. C. F., and Murphy, F. D. Punch liver biopsy. *Arch. Int. Med.* **81**:832-858, 1948.
11. Roth, A. A., and Turkel, H. Technique of prostatic biopsy. *J. Urol.* **51**:66-68, 1944.
12. Silverman, I. New biopsy needle. *Am. J. Surg.* **40**:671, 1938.

MEDICAL PROGRESS

STUDIES ON THE RELATION OF PITUITARY-ADRENAL FUNCTION TO RHEUMATIC DISEASE*

GEORGE W. THORN, M.D.,† THEODORE B. BAYLES, M.D.,‡ BENEDICT F. MASSELL, M.D.,§ PETER H. FORSHAM, M.D.,¶ S. RICHARDSON HILL, JR., M.D.,|| STEPHEN SMITH, III, M.D.,** AND JOSEPH E. WARREN, M.D.††

DURING the past few years it has become increasingly evident that the adrenal cortical hormones exert a marked influence on a wide variety of metabolic processes in man. The over-all effects exerted by these hormones may be divided into three general groups: an electrolyte-regulating effect; the regulation of the rate of utilization of carbohydrate, protein and fat; and an androgenic and anabolic effect.

NATURE OF ADRENAL CORTICAL ACTIVITY

Electrolyte-Regulating Effect of Adrenal Cortical Steroids

This is characterized by urinary retention of sodium and chloride, increased excretion of potassium, increased plasma and extracellular fluid volume.[1] It has also been shown that desoxycorticosterone-like steroids decrease the concentration of sodium and chloride in sweat.[2] The most potent electrolyte-regulating adrenal steroid is 11-desoxycorticosterone, which has been synthesized. The 11,17-oxysteroids (Compounds E and F) exert a relatively weak sodium-retaining effect[3] (Fig. 1).

Unfortunately, there is no direct measurement of circulating "salt" hormone. Therefore, the activity of such steroids must be estimated indirectly, by changes in the renal excretion of sodium, chloride and potassium, by alteration in the mineral composition of thermal sweat and by changes in hematocrit and body weight.

Regulation of Intermediary Metabolism by 11-Oxysteroids and 11, 17-Oxysteroids

The second group of metabolic activities modified by the adrenal cortex involves the regulation of carbohydrate, protein and fat utilization, control of lymphoid tissue and circulating eosinophils. The administration of this type of compound is characterized by the following effects:

An increase in blood glucose level and liver glycogen stores.

An increased conversion of protein to carbohydrate (increased gluconeogenesis). Recent studies indicate that this effect is accomplished, not by an increased catabolism of body protein, but rather by diverting amino acid radicals to pyruvic acid and glucose (antianabolic effect).

An increased mobilization of depot fat and its enhanced utilization, thus sparing carbohydrate. An increased intestinal absorption of fat has been observed after the administration of this group of steroids, and although relatively unimportant calorically, it is of theoretical interest.

An increase in the renal clearance of uric acid, resulting in the excretion of large quantities of urate, both in normal subjects and in patients with gout.

A lysis of fixed lymphoid tissue and a transitory decrease in circulating lymphocytes. A somewhat more permanent effect is observed on the circulating eosinophils, which almost completely disappear from the blood during the period of action of the hormone.

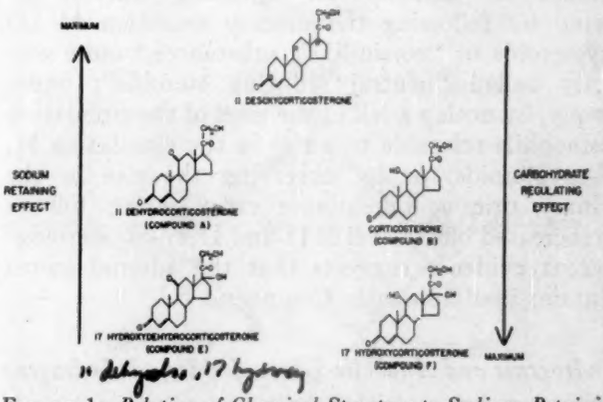

FIGURE 1. *Relation of Chemical Structure to Sodium-Retaining and Carbohydrate-Regulating Effect.*

*From the Medical Clinic, Peter Bent Brigham Hospital, the Robert Breck Brigham Hospital, the House of the Good Samaritan and the Department of Medicine, Harvard Medical School.

These studies were aided in part by a grant from the Committee on Research in Endocrinology, National Research Council, the Armour Laboratories, Chicago, Illinois, and the Upjohn Company, Kalamazoo, Michigan.

†Hersey Professor of Theory and Practice of Physic, Harvard Medical School; physician-in-chief, Peter Bent Brigham Hospital.

‡Associate in medicine, Harvard Medical School; visiting physician and director of research, Robert Breck Brigham Hospital; associate in medicine, Peter Bent Brigham Hospital.

§Instructor in pediatrics, Harvard Medical School; chief of rheumatic fever division, Children's Hospital; associate research director, House of the Good Samaritan; visiting physician, Beth Israel Hospital.

¶Instructor in medicine, Harvard Medical School; junior associate in medicine, Peter Bent Brigham Hospital.

||Assistant in medicine, Peter Bent Brigham Hospital; research fellow, Harvard Medical School.

**Research fellow, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital.

††Chief of medical department, House of the Good Samaritan.

Examples of the "carbohydrate-regulating" adrenal cortical steroids or "S" hormone are the 11-oxysteroids, Kendall's Compounds A[4] (11-dehydrocorticosterone) and B (Corticosterone) and the much more active 11,17-oxysteroids, Kendall's Compounds E[5] (17-hydroxy-11-dehydrocorticosterone) and F (17-hydroxycorticosterone), demonstrated in Figure 1. The effects on lymphoid tissue and eosinophils are exerted only by the 11,17-oxysteroids. In all but electrolyte effects, the latter substances are superior to the 11-oxysteroids and to 11-desoxycorticosterone. Although the salt-retaining effect of the 11,17-oxysteroids is approximately one thirtieth that of 11-desoxycorticosterone, adequate salt retention may be obtained by the use of relatively large quantities of these substances. It is therefore possible, with Compounds E and F, to maintain a satisfactory electrolyte balance in Addison's disease if adequate quantities of either of these hormones are administered. It appears that Compounds E and F may compete with 11-desoxycorticosterone in its action on electrolyte regulation. Thus, in the presence of excessive sodium retention induced by desoxycorticosterone acetate, treatment with large doses of Compound E may result, not in further sodium retention, but in increased sodium excretion.

One may achieve an approximate measure of the amount of "carbohydrate-regulating" factors secreted by following the urinary excretion of 11-oxysteroids or "cortin-like" substances,[6] more correctly called "neutral reducing steroids"; more simply, by noting a fall in the level of the circulating eosinophils referable to a rise in the circulating 11, 17-oxysteroids, or by observing the rise in the urinary uric acid-creatinine ratio, which follows an increased blood level of 11-and 11,17-oxysteroids.[3] Recent evidence suggests that the adrenal cortex contains predominantly Compound F.[7]

Androgenic and Anabolic Effect of Adrenal Androgens

The third group of adrenal steroids are those referred to as the adrenal androgens or "N" hormone. It is assumed that these substances exert an effect similar to that of the testicular androgens, which consists of masculinization, with retention of nitrogen, phosphorus, potassium, sodium and chloride.[8] This effect has been characterized as the androgenic or anabolic hormone effect. In the female it is evident that nearly all androgenic effect is derived from the adrenal cortical androgens, whereas in the male, the adrenal androgens appear to account for only two thirds of the androgenic substances, the remainder being derived from the testes. Adrenal androgens are related in structure to testosterone, but carry an oxygen group in position 11 (adrenosterone).

The secretion of androgenic substances or the administration of such steroids is evidenced by a relatively small rise in urinary 17-ketosteroids, their excretory product.

Practical Considerations in Adrenal Hormone Therapy

Two groups of adrenal cortical hormone preparations are available commercially at the present time*: whole adrenal cortical extracts derived from beef or hog adrenal glands and synthetic desoxycorticosterone acetate.

In cases of adrenal insufficiency, the salt-retaining factors are easily substituted for by the administration of synthetic desoxycorticosterone acetate (DCA) in the form of a solution in oil (5 mg. per cubic centimeter), a macrosuspension in various solvents, or in the form of subcutaneously implanted tablets or pellets weighing 125 mg. or 75 mg. each. Such pellets give off 0.5 and 0.3 mg., respectively, of DCA daily. These substances are ineffective in the therapy of rheumatic diseases.

Substitution therapy with "carbohydrate-regulating" factors has in the past been possible by the administration of whole extracts of beef or hog adrenal glands. Such commercial extracts contain relatively small quantities of the known steroid hormones. Aqueous whole adrenal extracts are about one tenth as potent as Lipo-adrenal Cortex (Upjohn), a concentrate of hog adrenal gland in oil, each cubic centimeter of which is equivalent to 2 mg. of Compound E. In the treatment of diseases such as rheumatoid arthritis, very large quantities of whole adrenal extract will obviously be required to induce an effect comparable to that obtained from 50 to 100 mg. of Compound E daily. By 1950 Compound E acetate should be available as a crystalline suspension in saline solution. Compound F, which has not been synthesized, is derived from hog adrenal glands. Doses of the same order of magnitude as Compound E acetate will probably be required in the treatment of rheumatoid arthritis. However, because of the greater solubility of Compound F, it will be necessary to increase the frequency of administration, as compared with Compound E acetate.

Pituitary Adrenocorticotrophic Hormone (ACTH)

Since purified pituitary adrenocorticotrophic hormone has become available in quantities adequate for clinical investigation, it has been possible to study the effect of administering this trophic substance on the secretion of adrenal steroids in man.[9,10]

**Whole adrenal cortical extracts* derived from beef adrenal glands, in aqueous solution, for intramuscular or intravenous use, assayed biologically, in 10-cc. and 50-cc. vials (for example, Adrenal Cortex Extract, Upjohn Company, Adrenal Cortex Extract, Wilson Laboratories, and Eschatin, Parke, Davis); and from hog adrenal glands in sesame oil, for intramuscular use, assayed against crystalline adrenal steroids, in 5-cc. vials (Lipo-adrenal Cortex, Upjohn Company — Oral preparations of adrenal cortical extract are available, but relatively ineffective in the doses employed). *Desoxycorticosterone acetate (DCA)* of synthetic source, in oil, for intramuscular use in 10-cc. vials (Cortate, Schering Corporation, Doca, Hoffmann-LaRoche, Incorporated: and Percorten, Ciba Pharmaceutical Products, Incorporated). Other DCA preparations include a water-soluble glucoside, pellets for subcutaneous implantation, macrocrystalline suspensions and sublingual tablets and solutions

Four hours after the injection of a single dose of 25 mg. of purified ACTH (Armour Standard*) there is a profound fall in circulating eosinophils and a rise in urinary uric acid excretion (increased ratio of uric acid to creatinine).[11] Repeated administration of ACTH, in doses of 10 mg., injected intramuscularly every six hours, 40 mg. daily (Armour Standard) has resulted in marked sodium and chloride retention, with initial potassium loss, a rise in urinary 11-oxysteroid excretion and in the level of circulating 11-17-oxysteroids as determined by biologic assay,[12] a rise in blood sugar level, a fall in circulating eosinophils, a rise in uric acid excretion and an increase in urinary 17-ketosteroid excretion to the upper limit of normal. Prolonged administration of the preparation gives rise to a chemical pattern and a clinical picture suggestive of mild Cushing's syndrome. Thus, in man, it appears

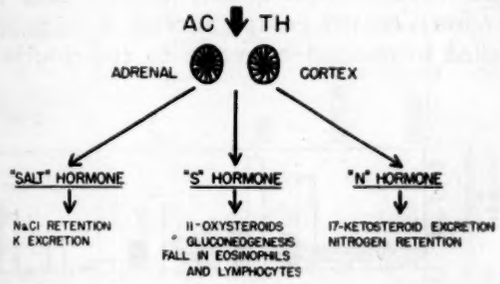

FIGURE 2. *Schematic Representation of the Effect of Adrenocorticotrophic Hormone (ACTH) on Adrenal Cortical Secretion.*

that, with an adrenal gland capable of responding, stimulation of the gland by ACTH is followed by an increased secretion of adrenal steroids, which give rise to all the known effects previously observed with crystalline adrenal steroid preparations (Fig. 2). The fall in circulating eosinophils affords the most sensitive indicator of adrenal cortical activation and may change before any of the other signs of adrenal cortical activation have become manifest. In addition to increasing the adrenal hormone level in patients with intact adrenal glands, ACTH stimulation has served a very useful purpose in providing a clear-cut test for adrenal cortical insufficiency.[11] Thus, patients with Addison's disease fail to show any of the effects mentioned above when given ACTH. Furthermore, the studies on patients with Addison's disease prove that the changes following ACTH are due to the secondary outpouring of the adrenal cortical steroids, rather than to a primary effect of ACTH itself. It is obvious, therefore, that the administration of ACTH would not be a suitable means for increasing adrenal hormone secretion in patients with adrenal cortical insufficiency due to primary disease of the adrenal gland or physiologic exhaustion.

*The ACTH used in these studies was supplied by Dr. John R. Mote, of the Armour Laboratories, Chicago, Illinois. The Armour Standard is of such potency that 4 gammas given intravenously to a hypophysectomized rat will lead to a fall in adrenal ascorbic acid of 20 to 40 per cent.

EPINEPHRINE STIMULATION OF THE ANTERIOR-PITUITARY-ADRENAL-CORTICAL SYSTEM

On the basis of earlier animal experiments by Long and others,[13, 14] in which it was shown that epinephrine was capable of stimulating an intact pituitary-adrenal-cortical system, studies in man were carried out.[15]

It was observed that a single injection of 0.3 mg. of epinephrine subcutaneously, in a patient with an intact pituitary gland and adrenal cortex, was followed by a fall in the level of circulating eosinophils, most marked after four hours. In normal persons, this amounted to 50 per cent or more; in patients with pituitary deficiency, or in patients with Addison's disease, a small or negligible fall was observed with this dose of epinephrine. The four-hour epinephrine test is a useful screening technic for detecting both anterior pituitary ACTH or adrenal cortical insufficiency (Fig. 3). Larger doses of epinephrine (1 mg. or more) appear to be capable of activating adrenal cortical remnants in patients with advanced Addison's disease, but not in patients with severe pituitary ACTH deficiency. Repeated injection of small quantities of

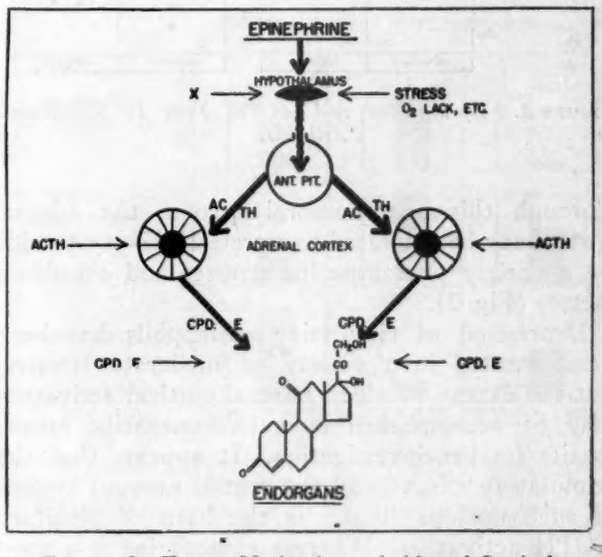

FIGURE 3. *Known Mechanisms of Adrenal Cortical Stimulation.*

epinephrine (0.5-0.8 mg.) every six hours over a period of weeks has resulted in a moderate stimulation of adrenal cortical steroid hormone production, as evidenced by eosinopenia, moderately increased urinary 11-oxysteroid excretion and a doubling of the urinary 17-ketosteroid excretion.

In contrast to the uninhibited stimulation of adrenal cortical hormones that follows the repeated administration of ACTH, epinephrine administration has the disadvantage of losing much of its

effectiveness as an adrenal cortical stimulator since endogenous ACTH production is inhibited by a rising titer of adrenal cortical steroids. This inherent disadvantage will be found with any substance that stimulates pituitary ACTH production.

Stimulation of the Hypothalamic-Pituitary-Adrenal-Cortical System by Stress

Anterior hypothalamic centers have recently been shown to form an essential link in the activation of pituitary ACTH secretion following conditions of stress, as well as epinephrine administration.[16] Upon nervous stimulation or contact with circulating epinephrine, a humoral substance appears to be secreted by cells of the anterior hypothalamus, which stimulates ACTH secretion.

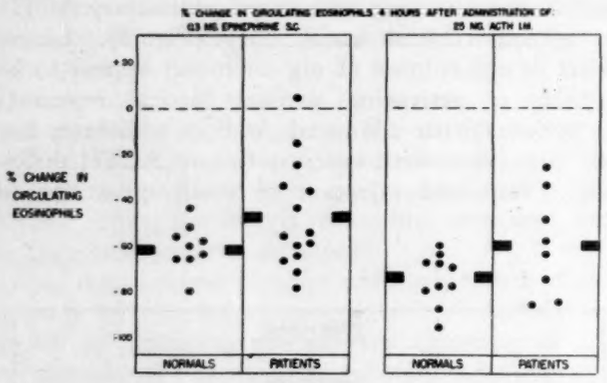

Figure 4. *Epinephrine and ACTH Tests in Rheumatoid Arthritis.*

Through this neurohumoral system, the adrenal cortex may be activated to secrete 11,17-oxysteroids by a variety of nonspecific stresses and emotional factors (Fig. 3).

Depression of circulating eosinophils has been demonstrated in a variety of moderate stresses, but the extent to which adrenal cortical activation may be accomplished by such nonspecific means awaits further investigation. It appears that the stimulatory effect upon the central nervous system of such noxious stimuli is the basis of pituitary ACTH activation. Whereas epinephrine is a good eosinolytic agent, nor-epinephrine is practically devoid of such action and is characterized pharmacologically by the near absence of any central-nervous-system stimulatory effect as compared to epinephrine.

Adrenal cortical reserve was measured by means of four-hour and forty-eight-hour ACTH tests, or both, in 22 patients with rheumatoid arthritis.[17] The four-hour ACTH test using the intramuscular injection of 25 mg. of ACTH and its effect on the circulating eosinophils four hours later was done on 10 patients, 8 of whom showed normal or low normal response (Fig. 4). One patient who did not respond subsequently proved to be refractory to therapy with ACTH as well. This essentially normal response in all but 1 of the group suggests that the available reserve of the adrenal cortex was not noticeably impaired by the rheumatic state. This concept was confirmed by the results of the forty-eight-hour tests, which in most cases were a continuation of the four-hour tests and were carried out using 10 mg. of ACTH every six hours. All the known functions of the adrenal cortex were stimulated in all but 1 of the 10 patients.

The epinephrine test, which consists of the administration of 0.3 mg. of epinephrine subcutaneously and determination of the fall in eosinophils at the end of four hours, was carried out on 14 patients with rheumatoid arthritis. The average fall of 50 per cent was slightly less than that in a similar group of normal subjects, who showed a mean 64 per cent fall (Fig. 4). However, the spread of the results in the tests on patients with rheumatoid arthritis was considerably greater than that in the normal control group. Several of the patients who failed to respond normally to epinephrine responded well to ACTH. Such a dissociation may be fortuitous or else suggests a possible deficiency in the hypothalamic-pituitary link in adrenal cortical activation (Fig. 3).

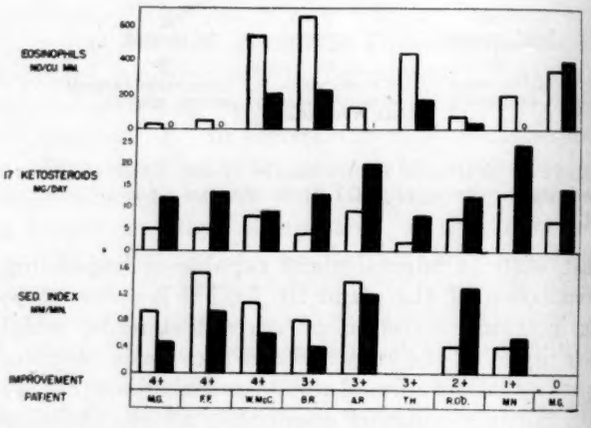

Figure 5. *Changes Following Forty-Eight Hours of ACTH Administration in Rheumatoid Arthritis.*

Effect of ACTH Therapy on Rheumatoid Arthritis

After the discovery by Hench, Kendall, Slocumb and Polley[18] of the Mayo Clinic, that Compound E, given in large doses (100 mg. per day), is effective in the treatment of rheumatoid arthritis, studies were made on the effect of the prolonged administration of ACTH to patients with rheumatoid arthritis. Ten patients were treated for from two to fourteen days with 40 mg. of ACTH per day, given in divided doses of 10 mg. every six hours. Of the patients treated, 5 were males and 5 females, varying in age from twenty-five to sixty-one years; the arthritis

was severe or moderately severe in 9 cases and mild in 1 case; and the duration of the disease varied from three months to twenty-eight years. In every case — that is, 9 — in which the adrenal cortex responded improvement occurred. Two patients were treated for two weeks, and 8 for forty-eight hours. Within twelve to twenty-four hours of the initial administration of ACTH, clinical improvement was observed, in every way similar to that reported by the Mayo Clinic group, who used 100 mg. of synthetic Compound E daily.[17] The most characteristic immediate change was loss of stiffness in the joints. This was followed by improvement

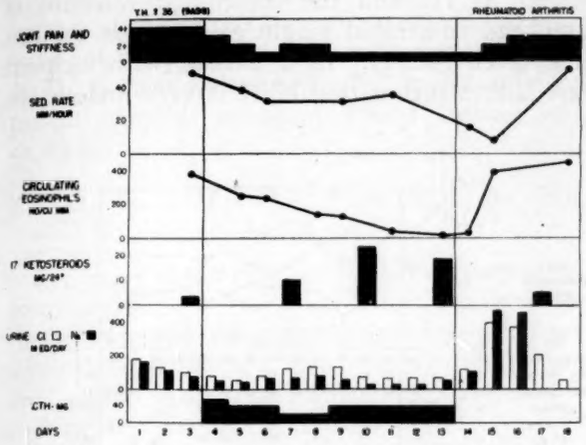

FIGURE 6. *Results of Treatment with ACTH.*

in the patient's general sense of well-being, culminating in a euphoric state. Since this is found in patients with Addison's disease on Compound E therapy it is not related solely to decreased pain on motion.[5] With more prolonged administration, there was increased range of motion in the joints and loss of pain. Objective evidence of improvement was found in a progressive fall in the blood sedimentation rate, often reaching normal levels after about a week. Evidence for a generally increased adrenal hormone secretion in these patients given ACTH was provided by a sustained fall in the level of circulating eosinophils, by a marked rise in 17-ketosteroid excretion and by sodium retention. Illustrative cases are shown in Figure 5 in their reaction to forty-eight hours of ACTH (95 mg.). It will be noted that the patient who failed to show any improvement on forty-eight hours of ACTH did not have an eosinophil fall, although urinary 17-ketosteroids rose. The patient who showed only 1+ improvement was the single one of the group whose arthritis was initially mild. A typical case on prolonged therapy with ACTH is presented in Figure 6.

Withdrawal of ACTH therapy after two to fourteen days of treatment in 10 patients was followed in twelve to twenty-four hours by a partial return of symptoms, including stiffness and pain in the joints, a rise in sedimentation rate and a loss of the euphoria.

Milder cases of rheumatoid arthritis show a somewhat more lasting effect after ACTH therapy, although the majority of cases return toward, but do not reach, their status before treatment.

The reversion to pre-treatment status may be minimized by withdrawal of the adrenal cortical stimulation gradually. Thus, after 10 mg. of ACTH intramuscularly every six hours, the same dose was given every eight hours for a week, then every twelve hours for another week, and then once a day for a short period before being discontinued altogether.

Because of the limited quantities of synthetic Compound E and natural ACTH that are available, attempts were made to increase the degree of pituitary adrenal stimulation by less specific methods. Since epinephrine has been shown to stimulate ACTH production in man, patients with rheumatoid arthritis were given a stimulating dose of epinephrine every six hours throughout the day and night. This therapy in 2 patients with rheumatoid arthritis resulted in a very slight but definite improvement, although, again, the maximum improvement observed was far less than that which occurred with ACTH or which might have been expected

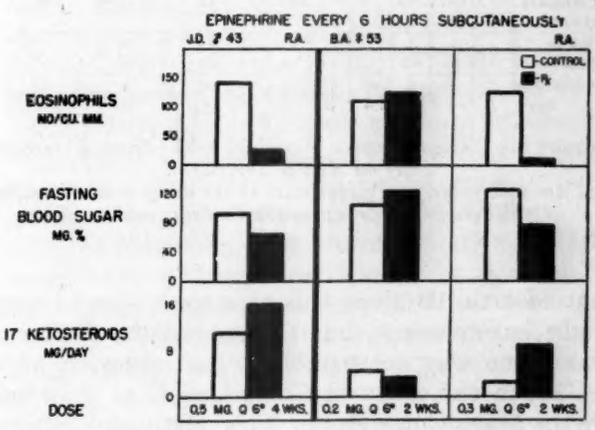
EPINEPHRINE EVERY 6 HOURS SUBCUTANEOUSLY
J.D. # 43 R.A.
B.A. # 53 R.A.
CONTROL
EOSINOPHILS NO/CU. MM.
FASTING BLOOD SUGAR MG. %
17 KETOSTEROIDS MG/DAY
DOSE
0.5 MG. Q 6° 4 WKS.
0.2 MG. Q 6° 2 WKS.
0.3 MG. Q 6° 2 WKS.

FIGURE 7. *Effect of Epinephrine Treatment on Subjects with Rheumatoid Arthritis.*
Note the ineffectiveness of a 0.2-mg. dose of epinephrine.

with 100 mg. of synthetic Compound E. Definite adrenal cortical activation occurred, although apparently not sufficient in terms of its beneficial effect on the rheumatoid arthritic state (Fig. 7). The use of epinephrine at the termination of a course of ACTH holds promise as a means of increasing endogenous ACTH production and of buffering the sudden falling off in adrenal cortical activity, which invariably follows the discontinuance of ACTH. A number of methods of nonspecifically stimulating the pituitary to increase its ACTH output, and thereby the adrenal cortical secretion, are now being studied in patients with rheumatoid arthritis.

In addition to the studies carried out with ACTH and epinephrine, an attempt was made to improve the clinical condition of patients with rheumatoid arthritis by the administration of large quantities of adrenal cortical extract. Two cc. of Lipo-adrenal Cortex (Upjohn) were given intramuscularly, every three or four hours, for one to three days, to 5 patients with rheumatoid arthritis. The total daily dose of Lipo-adrenal cortex was 12 to 15 cc. This corresponds to approximately 120 to 150 cc. of aqueous whole adrenal extract. Patients with rheumatoid arthritis given this treatment showed very slight improvement, but the magnitude of change was in no way comparable to that observed after ACTH in our group or Compound E as described by the Mayo Clinic group. This relative ineffectiveness appears, in all probability, to be due to the fact that the total amount of extract administered contained much less than the equivalent of 100 mg. of Compound E, or the quantity of Compound E or F released by the adrenal cortex upon stimulation by 40 mg. of ACTH, which was given in our studies.

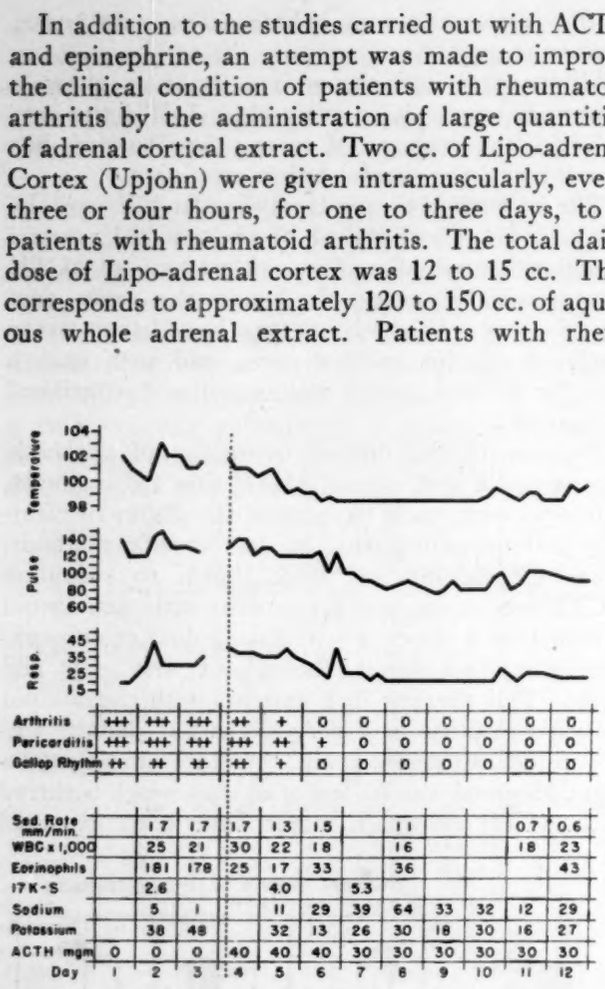

FIGURE 8. *Clinical Course of a Girl with Acute Rheumatic Fever on ACTH Treatment.*
Sodium and potassium values refer to the daily urinary output in milliequivalents on an approximately constant diet.

EFFECT OF ACTH ADMINISTRATION ON RHEUMATIC FEVER

The response to ACTH in patients with acute rheumatic fever is more striking than that obtained in patients with rheumatoid arthritis, in whom previous joint deformities persist in spite of ACTH-induced improvement. To date, 3 cases of acute rheumatic fever have been treated for periods varying from eight to fourteen days, with 10 mg. of ACTH given intramuscularly every six hours. An illustrative case in an eleven-year-old girl is shown in Figure 8. This patient was given ACTH early in her second known rheumatic attack, which was associated with subcutaneous nodules, arthritis, pericarditis and myocarditis, as suggested by a protodiastolic gallop rhythm and electrocardiographic changes. The patient was taken off acetylsalicylic acid three days before treatment with ACTH was begun. It will be noted that all the known adrenal cortical secretions appeared to be increased by ACTH, although the relative proportion by which the individual factors were augmented cannot be ascertained by current analytical methods. The posterior pituitary-like effect of Armour ACTH and the consequent retention of water lead to a rapid weight gain in most subjects being given ACTH. In a patient with incipient heart failure such a possibility is very undesirable.

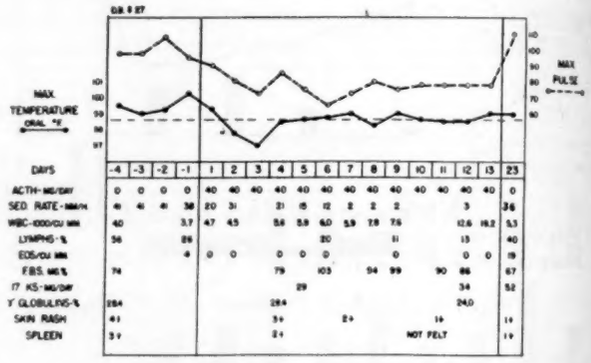

FIGURE 9. *Effect of ACTH on a Patient with Disseminated Lupus Erythematosus.*

However, in the limited number of cases treated and with the dose of ACTH employed, it was found that the improvement in cardiac efficiency, with its beneficial effect on renal circulation, led to an increased urinary volume, rather than to water retention during a period of a week. The over-all benefits were identical with those obtained with Compound E acetate.[19]

EFFECT OF ACTH ADMINISTRATION ON DISSEMINATED LUPUS ERYTHEMATOSUS

Three patients with acute disseminated lupus erythematosus showed marked clinical improvement, with rapid disappearance of the typical butterfly rash, when given 10 mg. of ACTH intramuscularly every six hours. A representative case is shown in Figure 9. The low initial eosinophil count, also found in another case, is a consequence of bone-marrow hypoplasia with normal adrenal cortical function, rather than a sign of greatly increased adrenal cortical activity as in Cushing's syndrome, in which a marked eosinopenia is diagnostic.[3] It should be noted that the gamma globulins, normally 12 to 14 per cent of the total protein, did not fall

below 20 per cent during the course of ACTH therapy, and yet the sedimentation rate was decreased and the patient was clinically improved.* It is also of interest that the initial, striking clinical improvement was obtained before any change in the circulating gamma globulins. Again, all major adrenal cortical functions appeared activated. Forty milligrams of ACTH was given daily for thirteen days, followed by 20 mg. daily for four days. Five days after discontinuation of ACTH therapy, the characteristic leukopenia, elevated sedimentation rate and enlarged, tender spleen returned. In spite of this, the patient was still feeling well, and the rash had not reappeared. The treatment had thus led to striking temporary improvement, which left the patient in a better clinical state but did not lead to a cure. Two subsequent ACTH courses following partial regression in this patient showed beneficial effects lasting up to six weeks.

Effect of ACTH Administration on Gouty Arthritis

In a study of the effect of ACTH on patients with gouty arthritis, it was found that treatment with the hormone caused a large increase in urinary uric acid excretion, with a concomitant fall in serum uric acid levels. The clinical improvement was striking and rapid. This improvement was characterized by increased joint mobility, decreased pain and softening of tophi. Although the rise in uric acid excretion was no greater than that achieved

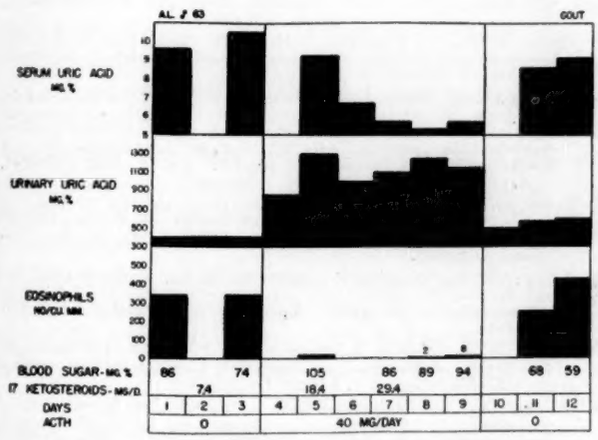
AL. J. 63
GOUT
SERUM URIC ACID MG.%
URINARY URIC ACID MG.%
EOSINOPHILS NO/CU. MM.
BLOOD SUGAR-MG.%
17 KETOSTEROIDS-MG/D.
86 74 105 86 89 94 68 59
74 184 294
DAYS 1 2 3 4 5 6 7 8 9 10 11 12
ACTH 0 40 MG/DAY 0

Figure 10. *Effect of ACTH on Severe Gout.*

by the administration of 5 gm. of acetyl salicylic acid per day,[20] the over-all clinical improvement was much more marked with ACTH administration. Upon withdrawal of ACTH, a mild gouty attack occurred after two days. This phenomenon has been reported by Hellman.[21] An illustrative case is shown in Figure 10.

*The electrophoretic analyses were carried out by Dr. W. F. Lever and Dr. J. McLean, of Harvard Medical School.

Discussion

Rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis may be viewed as related mesenchymal diseases, characterized by a nonspecific inflammatory reaction, presumably brought on by a peculiar susceptibility of the host to certain bacterial or tissue products.[22] Such pathologic states are apparently favorably altered by a sudden increase in the titer of circulating 11, 17-oxysteroids or related compounds of adrenal origin. With a sudden increase in the level of these steroids, the progress of the inflammatory reaction in heart, vessels and synovia is temporarily arrested. The majority of patients with these diseases seem to possess normal adrenal cortical reserve function, but appear incapable of increasing the activity of their adrenal cortex spontaneously. Is such an activation an essential part of the normal defense mechanism? If so, is it absent in those afflicted with mesenchymal disease? Or is the massive activation of adrenal cortical hormone production by ACTH merely a therapeutic implement acting favorably upon the patient's reaction pattern to the disease directly or by neutralizing some biologic antagonist? Evidence in support of this concept is the fact that 100 mg. of Compound E is needed to alter significantly the course of rheumatic diseases, whereas patients with complete adrenal insufficiency may be maintained with 10 to 20 mg. daily. Effective therapy is only attained when the level of hormone is increased, to supernormal levels.

Obviously, ACTH therapy will only be effective in patients in whom a normal adrenal cortical response is obtained. A marked decrease in circulating eosinophils following ACTH therapy is a valuable indication of increased secretion of 11,17-oxysteroids, which appear specific in their ability to depress circulating eosinophils[17] and lyse lymphoid tissue and which, to date, are the only type of steroid that has been shown to exert a beneficial effect in rheumatic disease.[18] Since they are synthesized from bile acids, the supply of these steroids will always be limited; therefore, a search for 17-oxysteroids derived from cholesterol or plant sterols and their trial in the rheumatic state is of great practical importance. ACTH, too, is limited by the number of pituitary glands available at any one time; thus, the search for effective nonspecific pituitary-adrenal stimulants must be continued.

The mode of action of 11,17-oxysteroids in these diseases is unknown. Improvement is observed in most patients within four to six hours. The blood sedimentation rate usually falls within forty-eight hours after treatment is begun, but the maximal change may not occur for ten to fourteen days. The initial changes that occur, such as loss of stiffness and increased capacity to move joints without pain, suggest a decrease in some "stiffness factor" and an immediate reduction in the chronic inflam-

matory reaction. A possible cause of these changes is the effect of the hormone on tissue permeability.[23] The singular specificity of adrenal steroids in their action on rheumatic diseases is suggested by the prompt response to Compound E and the ineffectiveness of desoxycorticosterone and dehydrocorticosterone acetate. Excessive DCA treatment in patients with Addison's disease is often associated with increased stiffness of the joints or arthralgia, or both.[24] It is of interest that Selye[25] has been able to accumulate a large amount of experimental evidence suggesting that arthritis is induced in rats by the administration of excessive amounts of desoxycorticosterone, a finding recently confirmed in man.[26]

The improvement in gout brought on by ACTH is apparently not due to increased renal uric acid clearance alone, but must also involve some direct effect on the joint tissue. Even though the effect of salicylates on the uric acid excretion is greater, the clinical improvement noted is far less than that with ACTH.

The dangers of continued ACTH or Compound E acetate treatment are principally the undesirable side-effects associated with a long-continued, high level of adrenal steroids. With chronic ACTH administration, one must be concerned with the possibility of persistent adrenal hyperplasia. Cushing's syndrome has been reported during the prolonged administration of Compound E.[17] On 40 mg. of ACTH per day this danger is minimal, and yet adequate adrenal cortical activation is achieved. With higher doses Cushing's syndrome is occasionally produced by ACTH as well. In all cases studied thus far on ACTH therapy there has been a rapid return of adrenal function to normal or subnormal levels. The pituitary ACTH mechanism is suppressed by exogenous ACTH and the adrenal cortex is stimulated, whereas with Compound E both the adrenal cortex and the anterior pituitary gland may become atrophic. Thus, withdrawal of Compound E therapy leads to a more acute, temporary adrenal cortical deficiency than the withdrawal of ACTH therapy. To minimize this sudden reduction in adrenal cortical activity, it appears desirable to administer ACTH for twenty-four to forty-eight hours after the withdrawal of Compound E therapy.

The beneficial effect of 11,17-oxysteroid therapy in the rheumatic diseases marks a great advance in therapy. Adrenal cortical hormone therapy does not, however, appear to affect the fundamental cause of the inflammatory changes that characterize these diseases. The use of adrenal cortical steroids or adrenal cortical stimulants will do much to further fundamental research in the field of rheumatic diseases. Their exact value as therapeutic agents remains to be worked out by long-continued therapy.

Summary

The major metabolic changes induced in man by adrenal cortical steroids are described. The remarkable observations of Hench, Kendall, Slocumb and Polley on the effect of Compound E therapy in patients with rheumatoid arthritis have been extended by the use of pituitary adrenocorticotrophic hormone (ACTH). The status of the adrenal cortical function was ascertained and found to be essentially normal in 16 of 21 patients with rheumatoid arthritis. There appears to be a wide variation in the state of adrenal cortical function from patient to patient, without apparent correlation with the severity or manifestations of the disease. In 9 patients with rheumatoid arthritis in whom pituitary adrenocorticotrophic hormone was capable of stimulating the adrenal cortex to increased activity, there was striking clinical improvement and a reversal of abnormal laboratory findings. Three patients with rheumatic fever and 3 with disseminated lupus erythematosus were similarly improved by ACTH therapy, as was 1 case of gout.

With the present inadequate supply of synthetic Compound E acetate and pituitary ACTH, nonspecific methods for stimulating an intact pituitary-adrenal system and naturally occurring adrenal cortical extract have been tried with little success in the treatment of rheumatic diseases.

References

1. Kendall, E. C. Influence of adrenal cortex on metabolism of water and electrolytes. In *Vitamins and Hormones: Advances in research and applications.* Edited by R. S. Hanes and K. V. Thimann. 6 vol. New York: Academic Press Inc., 1948. Vol. 6. P. 278.
2. Conn, J. W. Electrolyte composition of sweat: clinical implications as index of adrenal cortical function. *Arch. Int. Med.* **83**:416-428, 1949.
3. Thorn, G. W., and Forsham, P. H. Metabolic changes in man following adrenal and pituitary hormone administration. In *Recent Advances in Hormone Research* (in press).
4. Forsham, P. H., Thorn, G. W., Bergner, G. E., and Emerson, K., Jr. Metabolic changes induced by synthetic 11-dehydrocorticosterone acetate, including comparative studies with synthetic desoxycorticosterone acetate, natural 17-hydroxycorticosterone and lipo-adrenal cortex (preliminary report). *Am. J. Med.* **1**:105-131, 1946.
5. Thorn, G. W., et al. Clinical and metabolic changes in Addison's disease following administration of compound E acetate (11-dehydro, 17-hydroxy-corticosterone acetate). *Proc. A. Am. Physicians* (in press).
6. Talbot, N. B., Albright, F., Saltzman, A. H., Zygmuntowicz, A., and Wixom, R. Excretion of 11-oxycorticosteroid-like substances by normal and abnormal subjects. *J. Clin. Endocrinol.* **7**:331-350, 1947.
7. Haines, W. J., Johnson, R., Brunner, M., Pabst, M., and Kuizanga, M. Study of carbohydrate-regulating hormone of hog adrenal extract. *Federation Proc.* **8** (Part 1): 203, 1949.
8. Albright, F. Cushing's syndrome: its pathological physiology, its relationship to adreno-genital syndrome, and its connection with problem of reaction of body to injurious agents ("alarm reaction" of Selye). *Harvey Lect.* (1942-1943) **38**:123-186, 1943.
9. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Endocrinol.* **8**:15-66, 1948.
10. Mason, H. L., et al. Results of administration of anterior pituitary adrenocorticotropin hormone to normal human subject. *J. Clin. Endocrinol.* **8**:1-14, 1948.
11. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G. Test for adrenal cortical insufficiency: response to pituitary adrenocorticotropic hormone. *J. A. M. A.* **137**:1005-1009, 1948.
12. Halberg, F. *A Bioassay for Circulating 11-17 Oxysteroid* (to be published).
13. Long, C. N. H. Conditions associated with secretion of adrenal cortex. *Federation Proc.* **6**:461-471, 1947.
14. Vogt, M. Effect of chronic administration of adrenaline on suprarenal cortex and comparison of this effect with that of hexoestrol. *J. Physiol.* **104**:60-70, 1945.
15. Recant, L., Hume, D. M., Forsham, P. H., and Thorn, G. W. Studies on effect of epinephrine on pituitary-adrenocortical system. *J. Clin. Endocrinol.* (in press).

16. Hume, D. M. Role of hypothalamus in pituitary-adrenal cortical response to stress. *J. Clin. Investigation* **28**:799, 1949.
17. Hills, G., Forsham, P. H., and Finch, C. A. Changes in circulating leukocytes induced by administration of pituitary adrenocorticotrophic hormone (ACTH) in man. *Blood* **7**:755-768, 1948.
18. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. Effect of hormone of adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. *Proc. Staff Meet., Mayo Clin.* **24**: 181-197, 1949.
19. Hench, P. S., et al. Effects of adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (compound E) on acute phase of rheumatic fever: preliminary report. *Proc. Staff Meet., Mayo Clin.* **24**: 277-297, 1949.
20. Talbott, J. H. *Gout* Reprinted from *Oxford Loose-Leaf Medicine.* Pp. 79-134. New York: Oxford University Press, 1943.
21. Hellman, L. Production of acute gouty arthritis by adrenocorticotropin. *Science* **109**:280, 1949.
22. Baehr, G., and Pollack, D. Disseminated lupus erythematosus and diffuse scleroderma. *J. A. M. A.* **134**:1169-1174, 1947.
23. Opsahl, J. C. Influence of hormones from adrenal cortex on dermal spread of India ink with and without hyaluronidase. *Yale J. Biol. & Med.* **21**:255-262, 1949.
24. Thorn, G. W., Dorrance, S. S., and Day, E. Addison's disease: evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients. *Ann. Int. Med* **16**:1053-1096, 1942.
25. Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P. Hormonal production of arthritis. *J. A. M. A.* **124**:201-207, 1944.
26. von Pirozynski, W., and Akert, K. Polyarthritis und Nebennierenrindenhormone. *Schweiz. med. Wchnschr.* **79**:746, 1949.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35401

PRESENTATION OF CASE

A five-year-old boy was admitted to the hospital because of a chronic cough.

He had been seen in the Children's Clinic one year prior to admission, when his mother stated that several months before, the patient had a severe cold, which seemed to hang on longer than normal. This cleared after several weeks but was followed by a persistent cough productive of a small amount of sputum of unknown character. Otherwise the patient was active and well.

The past history was noncontributory. A sister, ten years old, had had tuberculosis at the age of two and a half years, apparently as a result of contact with a grandmother, who died of this disease two years before the patient was brought to the clinic. It was stated, however, that the patient himself had never been brought in contact with the grandmother.

Physical examination at the time of the clinic visit showed a well developed and well nourished boy. The chest was clear to percussion, but wheezes, groans and coarse breath sounds were heard over the right side posteriorly. The rest of the physical examination was negative.

A roentgenogram of the chest showed collapse of the lateral portion of the right middle lobe, with emphysema of the medial portion (Fig. 1). There was no evidence of mediastinal adenopathy.

Six weeks later the patient returned for bronchoscopy. The middle-lobe orifice was completely occluded by what looked like soft inflammatory tissue. There was reddening of the bronchus in this area. A biopsy taken at this time was subsequently reported as showing chronic inflammation. Subsequent appointments were not kept, and the patient was not seen again until his present admission.

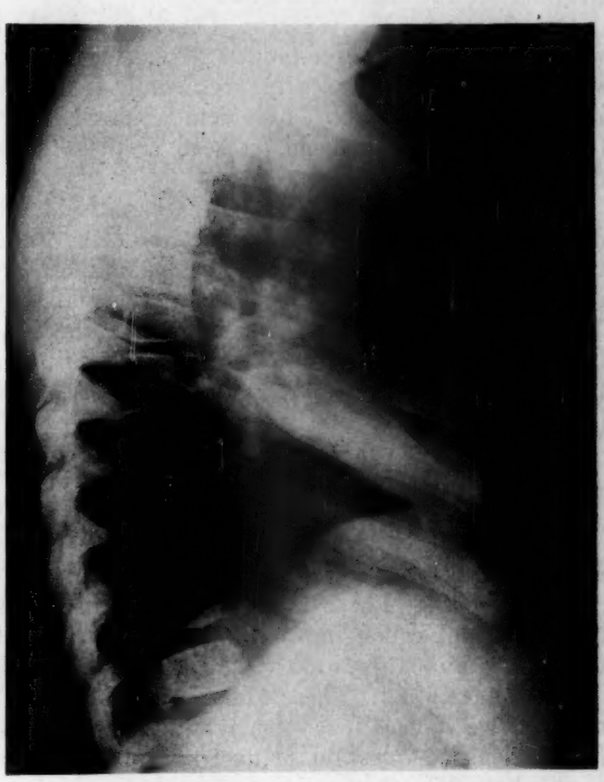

FIGURE 1.

At this time the chest was clear and the general physical examination was negative except for a few small, shotty lymph nodes in the axillary and inguinal regions bilaterally.

Examination of the urine was negative. The hemoglobin was 12.4 gm. and the white-cell count 11,000, with 47 per cent neutrophils, 46 per cent lymphocytes, 2 per cent monocytes, 4 per cent eosinophils and 1 per cent basophils.

A second roentgenogram of the chest showed continued evidence of involvement of the right

middle lobe, although the degree of atelectasis appeared less marked than on the previous examination one year before.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. William Berenberg: We have here the story of a five-year-old boy whose disease started when he was three and a half years old. During all this time his general health remained excellent despite a severe, persistent cough. At the time of his first examination all the physical signs were suggestive of some obstructive phenomenon in the bronchus, and this impression was corroborated by radiologic examination as well as bronchoscopy. May we see the chest films now?

Dr. Stanley M. Wyman: These films, which were taken over a three-month period, show very sharply defined, apparently segmental atelectasis in the right middle lobe, best demonstrated in the lateral view. The bronchi, as seen in these films, do not appear remarkable.

The second set of films, three months later, demonstrates definite clearing of the process. Films taken twelve days subsequently again show accentuation of the atelectasis and consolidation. This left anterior oblique film taken at the time of the original examination shows the right main bronchus, but unfortunately one cannot follow it down to the lower-lobe branches well.

Dr. Berenberg: Do you see any evidence of adenopathy?

Dr. Wyman: No.

Dr. Berenberg: At least there is no massive enlargement.

Dr. Wyman: There may well be small nodes, but I am not much impressed by them. I think that is a dubious question to settle in many cases.

Dr. Berenberg: These films do not add much to what we have already been told. We are thus faced with the question of determining the cause of this bronchial obstruction.

The likelihood of intrabronchial or pulmonary tumor is remote at this age. This benign course, negative biopsy, age and chest film make me believe that we need mention tumor only to exclude it.

The possibility of some congenital anomaly must be considered. The commonest malformations in this region are congenital stenosis and absence of cartilaginous rings. However, we lack the evidence of narrowing of the lumen necessary to consider this possibility seriously. Most patients with an anomaly of this type would not have remained asymptomatic for three and a half years. It would be difficult to explain the mass of soft inflammatory tissue occluding the middle-lobe orifice on this basis.

As one listens to the story, this case appears on the face of it to be a typical example of progressive bronchiectasis in a five-year-old boy following a respiratory infection that resulted in persistent pulmonic collapse. He may very well have had unrecognized pneumonia with persistent atelectasis and progressive bronchiectasis in the involved segments. The history and physical findings are both in keeping with this diagnosis. The type and duration of cough are typical. The observation that this child was well developed and well nourished is not surprising, since we see very few children at this age with bronchiectasis who are not well above the tenth percentile for weight. Most of these children look and act well.

We are told that the middle-lobe orifice, on bronchoscopy, was completely occluded by soft inflammatory tissue. I have not seen this occur in children with post-pneumonic bronchiectasis. We have seen plugging of course, but the plugging in bronchiectasis results from the accumulation of secretions, from inspissation or occasionally from a blood coagulum, which may fill or occlude a bronchial lumen. It therefore seems to me necessary to postulate another mechanism in addition to the bronchiectasis to explain the material found at bronchoscopy. There is no mention of a specific change in the microscopical section of the biopsied material. We must assume that it probably did not exist and that what is grossly described was just inflammatory tissue. It is my opinion that this patient had bronchiectasis, although it was probably secondary to the primary cause of the bronchial occlusion.

Dr. Benjamin Castleman: The report of that bronchoscopy was as follows:

> Biopsy attempted. Very little if any tissue obtained. Secretions aspirated. Some inflammatory tissue loosened, coughed up and saved for biopsy tissue.

Dr. Berenberg: I think even that is unusual for ordinary post-atelectatic bronchiectasis. One may see a good deal of mucosal reddening and some inspissated material but hardly that degree of true inflammatory reaction, especially without visible hilar adenopathy on x-ray study.

In a group of cases of the so-called "middle-lobe syndrome" recently reported following pneumonia of the right lower lobe there has occurred drainage into the perihilar region sufficient to produce significant adenopathy. This may result in obstruction of the middle-lobe bronchus with or without ulceration into the bronchial lumen. This syndrome could explain the picture here, but since there are only about 20 cases reported in children, I should hesitate to make this diagnosis without a well established sequence of events.

If this patient had tuberculosis, as we are invited to believe by the family history, he probably had intrabronchial disease. Certainly, one cannot even start to discuss the question of tuberculosis without asking a number of questions. Was a tuberculin

test done? Was the aspirated material smeared for acid-fast organisms? Was this material cultured for tuberculosis? If so, what were the results?

DR. CASTLEMAN: Nothing is left out, intentionally, but I do not believe there was a smear.

DR. ALLAN M. BUTLER: The tuberculin test in a dilution of 1:1000 showed swelling but no redness.

DR. BERENBERG: It seems extraordinary for swelling to occur without redness; one more often sees redness without swelling.

DR. BUTLER: It seems extraordinary, if it was questionable, that that point was not investigated further.

DR. BERENBERG: We have in the history the fact that this patient's sister and grandmother had tuberculosis. We have no information concerning the possible recent infectiousness of the sister. The statement that the patient had never been brought in contact with the grandmother may be misleading. Very often we obtain such a statement only to find that the patient was repeatedly shown to an infected grandparent and allowed in the same room although perhaps never held by her.

The state of well-being of this child is in keeping with intrabronchial tuberculosis at this age. Most children look the picture of health even with pulmonary lesions. Cough is not a common symptom in children with pulmonary tuberculosis as a matter of fact, but is a common symptom, of course, in intrabronchial lesions of any sort, including tuberculosis. Was fluoroscopy performed?

DR. WYMAN: No.

DR. BERENBERG: It might be interesting to know if the emphysematous area changed during respiration, in order to try to decide whether the emphysema was compensatory or otherwise. This might be helpful in deciding about tuberculosis. The nature and course of this lesion are in keeping with what one would anticipate with juvenile tuberculosis. The absence of visible hilar lymph nodes and a defined pulmonary lesion are not at variance with this possibility. The presence of a few small, shotty inguinal and axillary lymph nodes is not unusual in any five-year-old child.

The interpretation of the aspiration biopsy is rather difficult. The amount of material one gets from the bronchial aspiration of the tiny lumen of a five-year-old child is limited, regardless of the lesion. If there was any nonspecific inflammatory reaction about a localized process, one would be more apt to aspirate that than the defined lesion. Most children with a tuberculous lesion of this type should be either considerably better or considerably worse in a year's time. It is not a static process and would ordinarily have cleared up or produced a bronchiogenic spread over this period. If smears had been done, it would have been most helpful because the incidence of positive smears from material obtained on bronchoscopy in intrabronchial tuberculosis is higher than that from material obtained in almost any other form of juvenile tuberculosis. Certainly one cannot exclude the diagnosis of tuberculosis on the information at hand, especially in the absence of a conclusively negative tuberculin test.

In any child with persistent cough, wheezing, atelectasis and evidence of bronchial obstruction, foreign body must be ruled out. In favor of foreign body is the patient's age. The commonest age is between three and five years. The fact that he had an upper respiratory infection at the onset does not bother me. In one way it is almost in keeping with this diagnosis because the incidence of aspiration is highest at the time of a common cold. I suppose that is because the child tends to have nasal obstruction and hence becomes a mouth breather. The deep inspiration following cough is conducive to the aspiration of any foreign body that the child happens to have in his mouth at that time. The clinical picture is in keeping with foreign body, and a negative bronchoscopy does not exclude the possibility of a tiny body imbedded in the wall or one lodged distal to the bronchoscopist's view. The thing that disturbs me is the fact that this disease was in the right middle lobe, which is an unusual site for a foreign body; the incidence in this lobe is only 6 to 8 per cent of all foreign bodies. The absence of a dramatic episode of coughing and choking is not unusual, especially since it might well go unnoticed in a child who then had a cold and cough. Nothing is mentioned of possible dental caries or preceding tonsillectomy. These are only two of many possible sources of aspiration to be considered. Putrefaction, if present, would favor the likelihood of aspiration, but its absence does not exclude it since any number of foreign bodies do not cause putrefaction.

I would favor the diagnosis of bronchiectasis secondary to the aspiration of a foreign body but am unable to exclude the possibility of tuberculosis without more evidence than that at hand. In addition, this child had pulmonary atelectasis.

DR. BUTLER: Does Dr. Sweet want to say a word?

DR. RICHARD H. SWEET: When the patient was first seen on the Pediatric Service, the question of foreign body was considered and eliminated on the basis of bronchoscopic examination. I saw the boy at a later stage, and to me it was a classic picture of involvement of the middle-lobe bronchus secondary to peribronchial lymphadenitis. We have seen a large number of cases like that. We have not always proved them to be due to tuberculosis. We all have seen the other group of which Dr. Berenberg spoke, and I was surprised to hear it said that the number of reported cases was so small. We have an appreciable number here at the hospital, but no one thought to report them as a group. It is interesting in this patient that one bronchial segment was collapsed and the other

emphysematous. That was obvious at operation.

The peribronchial lymph nodes were not enlarged but were very much involved in a marked peribronchial infiltration. The artery and vein of the middle lobe were obscured by an infiltrative type of tissue, making dissection difficult and rather perilous, although we were able to isolate the vessels after much painstaking dissection, tying them independently. In doing that, I discovered that one of the lymph nodes was calcified, and I then remarked that it was probably on a tuberculous basis. The patient made a good recovery and has gone home.

FIGURE 2.

DR. CASTLEMAN: Do you see any specks that might be calcified lymph nodes?

DR. WYMAN: No; not even knowing the story.

DR. BUTLER: Would you have operated if he had had positive smears for tuberculosis?

DR. SWEET: I would not hesitate to do so because I think he is far better off with the middle lobe out.

CLINICAL DIAGNOSIS

Bronchiectasis, right middle lobe.

DR. BERENBERG'S DIAGNOSIS

Bronchiectasis, due to foreign body.

ANATOMICAL DIAGNOSES

Bronchial stenosis (middle lobe, lateral division) produced by calcified tuberculous lymph nodes.

Pulmonary atelectasis, middle lobe, lateral segment.

Miliary tubercles of lung.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This is the entire middle lobe (Fig. 2). From this specimen, one can see that one segment, which corresponds to the atelectatic portion on the x-ray film, is completely collapsed, whereas the other segment appears normal. The cause of the obstruction in the collapsed segment is a small tuberculous calcified lymph node pushing against the bronchus but not eroding into the lumen. In the lateral portion of the segment is a large caseous and calcified area of tuberculosis, which is, I believe, the primary focus. An interesting and unexpected finding was the presence of small miliary tubercles, in both the collapsed and the aerated segments of the lobe, so that there must have been a hematogenous spread. Some of these tubercles seem to be active, but others are fairly old. We were unable to find any actual tuberculosis within the bronchus. At the point of obstruction the mucosa seemed to be intact.

DR. SWEET: It is purely a matter of pressure upon the bronchus from the exterior.

DR. CASTLEMAN: Yes.

CASE 35402

PRESENTATION OF CASE

A sixty-six-year-old Italian-born man entered the hospital for the first time complaining of cough and chest pain.

He had enjoyed good health until four or five months before, when he experienced the onset of a hacking cough. This was persistent and soon became productive of white, mucoid sputum. Two months before admission he began to suffer pain over the left anterior thorax. This was at first present only on severe coughing but rapidly became more severe until he was aware of pain at all times but particularly on deep breathing or with the slightest cough. The pain was nonradiating in character and was unaltered by external pressure to the chest wall. With the onset of chest pain he experienced increasing anorexia and weakness. As his symptoms progressed his cough became more productive until he was bringing up half a cupful of white sputum daily. A few weeks prior to admission he noted a change in pitch and timbre of his voice. There was a weight loss of 25 pounds since the onset of the illness. Hemoptysis, dyspnea, chills, fever and night sweats were specifically denied. A review of the systems was otherwise

negative. No history of exposure to tuberculosis or to the various pathogenic dusts could be obtained. The patient had smoked two or three packages of cigarettes daily for thirty years but had voluntarily discontinued tobacco one month before admission.

Physical examination revealed a chronically ill man with signs of recent weight loss. There was no cyanosis or lymphadenopathy. The left pupil was larger than the right, but neurologic and ophthalmologic consultants denied the presence of a Horner syndrome. The trachea was not deviated. Dullness to percussion and diminished breath sounds were elicited over the anterior and posterior aspects of the left upper thorax. Fine rales were heard over both lung bases posteriorly. The heart was not enlarged, and there were no murmurs. There was a fullness in the right upper quadrant of the abdomen palpable three fingerbreadths below the costal margin. The spleen was not felt, and there was no abdominal tenderness. The prostate was three times the normal size, firm, regular and free of nodules. The fingers of the left hand had been amputated traumatically several years before. There was well developed clubbing of the remaining digits, with mild cyanosis. No peripheral edema was noted. There was weakness of the right lower facial nerve, but neurologic examination was otherwise negative.

The temperature was 99.2°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The hemoglobin ranged from 13.0 to 11.4 gm., and the white-cell count from 41,000 to 57,500, with an average differential of 93 per cent neutrophils, 3 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. Many band-form neutrophils were seen, but the morphology was not altered otherwise. A sternal-marrow aspiration contained 85 per cent myeloid cells, 12 per cent erythroid elements and 4 per cent plasma cells. The myeloid-erythroid ratio was 8:1. A shift to the left in the myeloid series was described. Urinalysis showed a specific gravity of 1.022, a ++ test for albumin and no Bence–Jones protein, and there were 2 or 3 red cells and 3 to 5 white cells per high-power field and occasional casts in the sediment. The stools were guaiac negative. The spinal-fluid protein was 54 mg. per 100 cc. The cell count was negative. The serum protein was 6.83 gm. per 100 cc., with an albumin of 3.19 and 2.85 gm. and a globulin of 3.98 and 3.64 gm. per 100 cc. The nonprotein nitrogen was 28 mg. per 100 cc. The alkaline phosphatase was 12.1 units per 100 cc. The calcium was 9 mg. per 100 cc. The prothrombin time was 70 per cent of normal. The sputum cultures grew out colon bacilli and *Haemophilus influenzae*. Three cytologic examinations of the sputum were negative.

The chest x-ray films showed a flame-like area of increased density extending from the left lung root, which occupied the central half of the left chest and obscured the left border of the heart. A bone series showed no evidence of metastatic lesions, but there were moderate degenerative hypertrophic changes of the spine.

Throughout his hospital stay the patient exhibited a slowly rising temperature reaching 102°F. by the eighteenth day, after which it varied between 104 and 105°F. The pulse varied between 80 and 120. Respirations were consistently elevated between 25 and 40. Large doses of penicillin and streptomycin failed to alter the febrile course. A spinal puncture revealed clear spinal fluid under normal pressure. Jugular compression on the right side failed to elevate the pressure. Bronchoscopy showed narrowing of the terminal portion of the left-lower-lobe bronchus, with incomplete fixation. No intrinsic masses were seen, and the remaining bronchi appeared unaltered.

On the eleventh hospital day it was noted that the patient's voice had become increasingly hoarse, and that his speech was thick. Slowly progressive mental deterioration occurred, and he declined rapidly following a distinctly septic course, which terminated in death on the twentieth hospital day.

Differential Diagnosis

Dr. John R. Graham: I should like to review this patient's history at the end of his first day in the hospital. So far, we have a five-month story in a sixty-six-year-old man, the essential points of which are: chronic cough, chest pain, increasing amounts of sputum, weight loss, weakness, nausea and the development of a change in his voice. That story, in itself, certainly makes one think very strongly of carcinoma of the lung. The physical examination, which was done on entry to the hospital, was perfectly consistent with such a diagnosis. The chest findings, the mass in the right upper quadrant, and the suggestion of some cerebral lesion are all perfectly consistent with that diagnosis also.

Before going on with the rest of the story, I wonder if we may look at the x-ray pictures made on the second day.

Dr. Stanley M. Wyman: The chest examination is a film taken with a portable apparatus showing an irregular area of density in the left midlung field. It seems to radiate out peripherally, and there is a suggestion of some mottled density in the right lung. The next examination, eleven days later, is more satisfactory and better demonstrates the central area of density, which in the lateral view appears to be located anteriorly, probably in the left upper lobe. Again, one sees indefinite areas of mottled density in the right lung throughout its entire distribution. There are old fractures of several right ribs, and probably several fractures on the left as well. It is impossible to trace the bronchial tree well on these films because of respiratory motion. The last films, which were taken in a search for metastases, show no definite bone destruc-

tion but they do show rather extensive degenerative changes in keeping with the patient's age and probable occupation.

DR. GRAHAM: There were no subsequent films of the chest?

DR. WYMAN: These are all; apparently, no subsequent films were taken.

DR. GRAHAM: I paused at that point because it seemed to me so far that this history was a fairly characteristic one, and that it is only as we go on that the diagnosis becomes involved. What had seemed to me a rather straightforward story is now complicated by some atypical findings and happenings. In the first place, the blood picture is unusual — the high white-cell count with the high percentage of neutrophils is certainly an unusual finding, and one's first thought is whether there was some fundamental blood dyscrasia, intrinsically connected with the lesion in the chest. One might wonder if the patient had a form of leukemia, with a chest complication. However, I think that the blood picture and the marrow findings were really not strikingly abnormal, showing a bit of a shift to the left in the white-cell series rather than a marrow full of very young leukemic cells. It does not really fit in with the diagnosis of leukemia — certainly not leukemia in the stage in which the patient appeared. He did not have a large spleen, an important lack that militates against that diagnosis. He had no significant anemia, so often present in leukemia. I am assuming rightly or wrongly that his voice changes were intrinsically connected with the mass in the chest and were based on involvement of the recurrent laryngeal nerve. We are not told what the vocal cords showed. I think the laryngeal involvement is unusual in the course of leukemia, even if the disease involves the lung. I am therefore betting against leukemia. I am more inclined to think that the high white-cell count and the increase in neutrophils were probably an accentuated response to infection.

There is one other thing that crosses my mind. In the days when we were using more sulfonamides, we used to see an occasional patient with a very high white-cell count. I remember one here with a count of 72,000, and others up to 100,000 have been reported as a response to sulfonamides. I wonder if by any chance this man had been given such a drug before entry to the hospital.

Other things that bothered me were the increasing fever and the general septic course. They did not respond to the ordinary, apparently adequate chemotherapy. This raises the question of whether he had a disease that was nonbacterial in origin — either virus or fungus. I also wonder whether he had disease involving some center in the brain that has to do with temperature regulation. In connection with this one immediately begins to think of the possibility of a Hodgkin lesion, which we know will cause fever and occurs as an isolated finding involving the chest occasionally. I have not seen this type of blood-picture response to Hodgkin's disease, although one has to admit that the presence of eosinophils with this high white-cell count is rather an unusual finding in a leukocytosis due to infection; consequently, Hodgkin's disease with its accompanying eosinophilia has to be considered. Against the possibility of Hodgkin's disease is the rather progressive course of the illness in the absence of an enlarged spleen, and the lack of any obvious lymphadenopathy elsewhere.

One, of course, has to think of all the other lung diseases, tuberculosis, empyema, abscess, and bronchiectasis, which do not particularly look like this in my estimation, and even some of the fungous diseases or histoplasmosis, which could possibly produce this type of picture. I see no evidence in their favor.

I am brought back to the original diagnosis of carcinoma of the lung probably arising from a small bronchus or the alveolar cells, with involvement of the recurrent laryngeal nerve from regional lymph nodes, and very likely some involvement of the brain and liver and possibly even the kidneys. Simpson* reported a collection of cases of carcinoma of the lung some years ago in which the most common metastases were to the bones, regional lymph nodes, liver, brain, kidneys and adrenal gland, various other organs being affected also, but these were the most important and in about that order. In favor of difficulty with the liver we have some laboratory findings, that are significant — the inverted albumin-globulin ratio, the high alkaline phosphatase and the slightly disordered prothrombin time. It is hard to guess about the kidneys, since there was only one urine report, which showed albumin and a few red cells. This may have been a result of metastases to the kidney or a response to what I think must have been the cause of his fever — namely, secondary infection with some organism not sensitive to the antibiotics used.

I will end up with a diagnosis of carcinoma of the lung with metastases in the liver and probably elsewhere, in addition to secondary infection, most likely arising in the area of the tumor, and terminal septicemia.

We are told that he had an enlarged prostate. From the description it apparently was not a malignant lesion but simply prostatic hypertrophy.

A PHYSICIAN: Was the serology reported?

DR. BENJAMIN CASTLEMAN: I am sure it was taken, but the report was not put in the record.

DR. JAMES H. TOWNSEND: I wonder if he had a large carcinomatous abscess behind an obstructed bronchus that was responsible for this high leukocytosis?

DR. CASTLEMAN: A straight abscess?

*Simpson, S. L. Primary carcinoma of lung. *Quart. J. Med.* 22:413-432, 1929.

DR. TOWNSEND: Yes, abscess arising from the tumor.

DR. ANDRIES QUERIDO: I should like to comment about the leukocytosis. Such an extremely high leukocytosis is usually infectious in origin, either streptococcal or staphylococcal, but in such cases eosinophils are absent. The only other condition that I know of in which it is found and in which eosinophils are present is a highly necrotizing tumor, not an abscess. The white-cell count may go as high as 50,000 or 60,000. First of all, this illustrates that it is very worth while to count the eosinophils per cubic millimeter. It is a very easy thing to do. If this patient had 500 eosinophils per cubic millimeter, I would say, not abscess, but a highly necrotizing carcinoma.

A PHYSICIAN: Is it not true that carcinomas, particularly those of the kidney and liver, give rise to a high white-cell count without infection?

DR. CASTLEMAN: Yes, increased white-cell counts occur in renal-cell carcinoma, carcinoma of the lung and primary hepatoma.

DR. QUERIDO: An eosinophilia in hepatoma.

DR. CASTLEMAN: In hepatoma it is possible to find thrombi in the hepatic veins, and even in the portal radicles, which might account for some necrosis.

CLINICAL DIAGNOSES

Carcinoma of lung?
Pseudoleukemia.

DR. GRAHAM'S DIAGNOSES

Carcinoma of lung, with metastases in liver, probably elsewhere.
Secondary infection.
Terminal septicemia.

ANATOMICAL DIAGNOSES

Carcinoma of lung, undifferentiated, upper lobe, with extensive necrosis and with metastases to lungs, bronchial lymph nodes, liver, adrenal glands, and brain.

Atelectasis, compression type, posterior apical and superior lingular segments, upper lobe of left lung.
Bronchiectasis, chronic, severe.
Pulmonary osteoarthropathy, severe.
Myeloid hyperplasia of bone marrow.
Atherosclerosis, coronary artery and aorta, moderate.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This patient's tumor was, as seen on x-ray study and as Dr. Graham predicted, in the left upper lobe and was a solid mass that extended anteriorly and, in fact, went over the midline a bit. The tumor was extremely necrotic, not a true abscess, but merely necrosis of tumor. There was only one metastatic nodule close to the tumor and several metastatic nodules throughout the other lung. The anterior and mediastinal extension of the tumor was really extension rather than metastases to regional lymph nodes. There were numerous metastases to the liver, which accounted for the high alkaline phosphatase and other impaired liver-function studies. There were metastases to both adrenal glands, but none to the kidneys. The tumor was an undifferentiated one; in places it looked almost sarcomatous, with spindle-shaped cells. Mitoses were very common, and many cells had four or five nuclei such as one sees in undifferentiated sarcoma. On the other hand, when one studied the metastases where the tumor was not as undifferentiated, the cells were unquestionably of epithelial origin so that one would call it an undifferentiated carcinoma rather than an oat-cell, adenocarcinoma or squamous-cell lesion, which are the more usual types seen.

DR. GRAHAM: How about the brain?

DR. CASTLEMAN: It measured 5 mm. in diameter in the left superior frontal gyrus.

DR. QUERIDO: Was the kidney stained for amyloid?

DR. CASTLEMAN: No, but there was nothing to suggest amyloid in the routinely stained sections.

DR. GRAHAM: I think that the fever was explained by the process that Dr. Querido has suggested. That is interesting. More attention ought to be paid, perhaps, to the eosinophil count.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. Carroll B. Larson, M.D.
Robert M. Green, M.D. C. Stuart Welch, M.D.
Dwight O'Hara, M.D. Vernon P. Williams, M.D.
Fletcher H. Colby, M.D. Benjamin Castleman, M.D.
Robert L. Goodale, M.D. Hugh R. Leavell, M.D.
Chester M. Jones, M.D. J. Englebert Dunphy, M.D.
Harvey R. Morrison, M.D. Charles H. Burnett, M.D.

SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

REPORT OF THE HOOVER COMMISSION REVIEWED

THE duties of the Commission on Organization of the Executive Branch of the Government, known as the Hoover Commission, were "to investigate activities of the Executive Branch with the objectives of limiting expenditures as far as possible consistent with proper performance of essential services; doing away with overlapping and duplication; consolidating similar services and abolishing unnecessary ones; and defining the limits of executive function."

An analysis of the report of the Committee on Medical Services of the Commission was presented at the annual meeting of the Massachusetts Medical Society by Professor Hugh R. Leavell of the Harvard School of Public Health and appears as the leading article in this issue of the *Journal*.

When the report was first released it became immediately apparent that the federal Government was spending far too much money on medical and public-health operations, most of the expenditures being made by the Veterans Administration, the armed forces and the Federal Security Agency. The taxpayer may well be aghast at the medical bill of $1,250,000,000, incurred in 1948, even accustomed as he has become to governmental extravagance.

The chief present weaknesses in the health services are in the medical-care program rather than in public health and research. This consists of competition between agencies for scarce personnel, wasteful construction of hospitals without over-all planning, and failure to utilize existing facilities to the best advantage. A lack of centralized responsibility for the over-all federal health plan has resulted in the competition among agencies for scarce medical and technical personnel and in hospital construction regardless of the plans or needs of other agencies or of state and local facilities. Construction costs range from $20,000 to $51,000 per bed, with voluntary hospital construction estimated at about $16,000 per bed. The dollar has apparently two values — fifty cents to the average citizen, and a quarter when spent by the Government! The geographic location of Veterans Administration Hospitals has also been unwise, and the policy regarding beneficiaries of federal medical service is unclear.

The recommendations of the report specify in particular a united medical administration to have control of Veterans Administration hospitals, general, post and station hospitals of the armed forces within the continental United States, the entire Public Health Service, nonmilitary hospitals in the Canal Zone, and hospitals of the Food and Drug Administration. At its head should be "the ablest health and medical administrator obtainable," who would be appointed by the President and confirmed by the Senate.

Congressional action should define clearly those who are entitled to the benefits of Government care, and a survey should be made to determine the amount of federal assistance that is necessary for medical and health education.

Research, preventive medicine and public health—all of which are factors in the prevention of disease—should be given high priority. The best way of lowering the costs of medical care is to decrease the need for it.

Although the Commission was divided on this point, the consensus of opinion was in favor of an independent health agency at the present time, rather than one that would combine health, education and security. Such a combination, however, might be eventually desirable.

THE ADRENAL GLAND AND THE RHEUMATIC STATE

THE discovery by Hench and his collaborators[1, 2] of the remarkably beneficial effect of a particular adrenocortical steroid (compound E or Cortisone) on the course of rheumatoid arthritis and rheumatic fever has been amply confirmed and must be classified as one of the significant achievements of modern medicine. Elsewhere in this issue of the *Journal* Thorn and his associates show that stimulation by anterior pituitary adrenocorticotrophic hormone (ACTH or ACTARMOUR) is equally effective by inducing the secretion of substances similar to compound E by the patient's own adrenal glands. The striking improvement in symptomatology and the establishment of an almost euphoric state in patients with rheumatoid arthritis or rheumatic fever far surpasses the effects of any of the conventional drugs now employed. It is already apparent, however, that withdrawal of therapy may precipitate recurrence of symptoms, particularly in patients with rheumatoid arthritis. This suggests that the primary cause of the rheumatic state is not affected by adrenal-hormone therapy, although the manifestations of the disease are completely abolished.

Studies on the state of adrenocortical function in patients who subsequently respond to treatment do not permit one to postulate *absolute* adrenocortical insufficiency as a prerequisite to the development of the rheumatic state. In fact, rheumatoid arthritis is rarely seen among untreated patients with Addison's disease. The very large dose of Cortisone (100 mg. daily) required to initiate a therapeutic response may lead to the development of Cushing's syndrome, a manifestation of adrenocortical overactivity, when the drug is administered for periods exceeding two weeks. The effective therapeutic dose thus exceeds the quantity produced by the adrenal glands under normal circumstances. This suggests that the effect in rheumatoid arthritis represents a pharmacologic action of the hormone. The presence of factors inhibiting the normal physiologic action of Cortisone in patients with rheumatic disease must also be considered.

The rapid and dramatic improvement that follows therapy forms a unique opportunity to investigate the pathogenesis of these hitherto baffling disorders. The rapidity with which initial improvement is noticed (often within six hours of the injection) raises interesting speculation concerning the mechanism by which the course of such persistent and chronic disorders as rheumatoid arthritis, disseminated lupus and rheumatic fever is modified.

It is apparent that, in contrast to Cortisone, improvement in these disorders with ACTH therapy presupposes the capacity of the patient's own adrenal glands to produce large quantities of hormone for prolonged periods. It is to be anticipated that under certain circumstances adrenocortical reserve might be low, and ACTH therapy hence would be relatively ineffective. With both drugs undesirable side effects resulting from excessive adrenal-hormone therapy must be anticipated. The adrenal glands of patients treated with Cortisone will presumably undergo compensatory atrophy during the period of therapy, whereas with ACTH treatment there will be marked hypertrophy and hyperplasia. With both drugs the function of the anterior pituitary body, at least in the production of ACTH, will be depressed. It appears that the adrenal gland and pituitary body return to their normal state within a few days of the discontinuance of therapy.

To date Cortisone and the closely related 17-hydroxy-corticosterone or compound F have proved to be by far the most effective antirheumatic agents, making them practically specific. Cortisone, being derived from bile acids by a twenty-four-step chemical procedure, is limited in amount and of necessity very expensive. An active search for other sources of more immediate precursors of Cortisone has led

to their discovery in an African strophanthus plant and a Mexican yam. ACTH is, at present, derived from the pituitary body of domestic animals, the hog in particular. Some 4000 hogs will yield enough ACTH to treat one patient for twenty days. In the present difficulty with totally inadequate supplies of Cortisone and ACTH for large-scale therapeutic use, the producers of these substances have adopted specific plans for the equitable distribution of the material.

Cortisone (Merck) is sold to competent investigators only after their specific requests to and acceptance by a committee appointed by the National Academy of Science. The requirements of the committee are such that the investigators must have adequate facilities for properly studying the over-all metabolic effects, mode of action and clinical influence of the hormone in various disease states. ACTH is distributed to competent investigators for the same purpose by the Armour Laboratories.

In the present search for other effective agents in the treatment of the so-called "collagen" diseases and in reviewing the older forms of treatment that have proved helpful in certain cases, one is constantly confronted with this question: Is the drug effective because of its specific pharmacologic action, or is it merely one of many agents capable of eliciting a nonspecific pituitary-adrenal response and thereby of increasing the level of circulating adrenocortical steroids temporarily? The studies of Selye et al.[3] leave no doubt that a wide variety of stresses initiate a response that is characterized by the liberation of pituitary ACTH and secondarily adrenocortical hormone. Any agent or procedure capable of eliciting this reaction in a patient with rheumatoid arthritis must be considered potentially capable of initiating a profound change in the course of the disease. Unfortunately, it is usually not possible to obtain an excess of adrenal hormone for prolonged periods by nonspecific means because of the depressing effect of a high level of circulating adrenal steroids on further pituitary-ACTH production.

Although it is too early to evaluate the ultimate clinical usefulness of these drugs in the treatment of rheumatic disease, there is no doubt that investigation in this field of disease has been given a tremendous stimulus. Furthermore, preliminary reports suggest that the usefulness of these hormones is not limited to the group of so-called "collagen" diseases, but that they have much more widespread value.

References

1. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. Effect of hormone of adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. *Proc. Staff Meet., Mayo Clin.* **24**: 181-197, 1949.
2. Hench, P. S., Slocumb, C. H., Barnes, A. R., Smith, H. L., Polley, H. F., and Kendall, E. C. Effect of adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (compound E) on acute phase of rheumatic fever; preliminary report. *Proc. Staff Meet., Mayo Clin.* **24**:277-297, 1949.
3. Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P. Hormonal production of arthritis. *J. A. M. A.* **124**:201-207, 1944.

UNIPOLAR ELECTROCARDIOGRAPHY

Electrocardiography is often said to be an empirical science, but it can hardly be termed static. The physician who labored long and hard to master the standard bipolar limb leads was not allowed to relax with his newly gained knowledge very long. The introduction of bipolar precordial leads into clinical practice, after much debate and in the face of considerable objection, made it necessary for him to continue to dig into the journals and newer textbooks in order to keep abreast of the field. Those who made the effort were not long in appreciating the great value of the innovation, particularly in the diagnosis of anterior myocardial infarction. As experience accumulated, the additional value of multiple precordial leads became apparent. As if this were not enough, the practice of taking bipolar leads was challenged, and the advantages to be gained by rendering one electrode indifferent were pointed out, originally by Wilson and later by Goldberger. Although some years have elapsed since Wilson introduced the technic, it has only recently begun to receive the attention it deserves.

The need for a more precise electrocardiographic method for determining relative right or left ventricular predominance has long been recognized. Inextricably bound up with the same problem is the question of how best to determine the position of the heart electrocardiographically, since, in many cases, enlargement of a ventricle greatly influences the position of the heart. With standard limb leads alone, there may be no way to differentiate changes due to alteration in the position of the heart

and those due to a damaged myocardium. Goldberger, by the use of augmented unipolar leads and by his emphasis on unipolar limb leads, has shown how unipolar electrocardiography may be the key to many problems involving changes in the position of the heart or enlargement of a ventricle, or both.

It is still too early to advocate the routine clinical use of unipolar limb leads, augmented or otherwise. Unipolar chest leads are used routinely by many electrocardiographers, and some knowledge of them is rapidly becoming essential. In the diagnosis of myocardial infarction it is doubtful that unipolar electrocardiography possesses any great advantage over bipolar methods. In anterior infarcts the standard bipolar limb leads and multiple precordial leads, either unipolar or bipolar, are likely to provide information of diagnostic value, particularly if serial studies are carried out. For the diagnosis of posterior infarcts the physician must still lean heavily on the standard bipolar limb leads. It seems likely, however, that when satisfactory standards for unipolar leads are developed and as experience grows, the technic may find a permanent place in the list of useful electrocardiographic procedures. The specific value of augmented unipolar leads is yet to be defined, but Goldberger's interpretation of unipolar limb leads should be borne in mind whenever information concerning the position of the heart is needed. The further development of unipolar electrocardiography is well worth watching by physicians interested in cardiology.

NATIONAL BIRTH STATISTICS

A RELEASE from Federal Security Administrator Oscar R. Ewing discloses that "a greater proportion of births in the United States were delivered in hospitals or institutions in 1947 than in any previous year on record."

The number of registered live births during 1947 rose to a peak of 3,699,940, with the proportion occurring in hospitals reaching a new high of 84.8 per cent.

Births attended by physicians were higher in urban than in rural areas, 98.0 per cent and 90.3 per cent respectively, and markedly higher in white (98.5 per cent) than in nonwhite (67.4 per cent) populations. Deliveries in Connecticut, Nebraska, New Hampshire and the District of Columbia were attended by physicians in 100 per cent of the cases, although in the District of Columbia, interestingly enough, 1.0 per cent of the births are also listed as having been attended by midwives. In Massachusetts and Vermont 99.9 per cent of cases were attended by physicians with no midwives participating in any case. In Mississippi physicians attended 61.4 per cent of the deliveries, midwives caring for the remainder.

It will be seen by our weekly report that the cholera is no longer in the city as an epidemic. Of the 5 deaths from the disease last week, 3 were individuals just arrived from other places. . . . Although its ravages here have been light compared with those of some other places, yet it has numbered over 600 victims during the three months of its prevalence, and has increased the mortality of the city, during some weeks, more than a hundred per cent. above the weekly average.

Boston M. & S. J., *October 3, 1849*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

HARTNETT — John H. Hartnett, M.D., of Worcester, died on May 10. He was in his seventy-fourth year.

Dr. Hartnett received his degree from Tufts College Medical School in 1911. He was affiliated with Belmont Hospital and St. Vincent Hospital. He was a fellow of the American Medical Association.

His widow, a son, two daughters, a brother and three sisters survive.

LAMBERT — John H. Lambert, M.D., of Lowell, died on September 10. He was in his seventy-fourth year.

Dr. Lambert received his degree from Boston University School of Medicine in 1899. He was formerly senior-surgeon at Lowell General Hospital and consulting roentgenologist at Bedford Veterans Administration Hospital. He was a former president of Middlesex North District Medical Society and was a member of the New England Roentgen Ray Society and the American Roentgen Ray Society and a fellow of the American College of Surgeons and American Medical Association.

His widow, three daughters, two sons and nine grandchildren survive.

MASON — Robert L. Mason, M.D., of Wellesley, died on September 20. He was in his fifty-third year.

Dr. Mason received his degree from Harvard Medical School in 1922. He was formerly chief of the surgical staff at Cushing General Hospital and a member of the staff of the Lahey Clinic. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow, a son and three daughters survive.

NOTES FROM THE MEDICAL EXAMINER

DETERMINATION OF THE BLOOD GROUPS OF DRIED BLOOD STAINS

The antigens A and B, which determine the classic blood groups, are relatively stable substances. Therefore, it is possible to determine their presence in dried blood stains and thus indirectly to determine the group of blood that produced the stain. The principle of this technic is as follows:

One allows a mixture of anti-A and anti-B reagent to react with the stain. The quantities of agglutinins in the reagent are carefully adjusted so that a stain that contains only a small amount of A, for example, will remove all the anti-A. The anti-B is similarly adjusted. These amounts are determined by preliminary tests on stains of known groups. The reaction is usually carried out with about 1 sq. cm. of material, such as stained cloth, finely cut up with scissors and mixed with the anti-A and anti-B reagent in a test tube. After this mixture has been allowed to stand overnight, preferably with occasional mixing during the interval, a drop of the liquid is taken off with a wire loop and is tested with Group A cells. A similar preparation is made with a loopful from the mixture and Group B cells. If Group A cells are agglutinated, but Group B cells are not, one may conclude that the following sequence of events took place: the anti-B in the reagent was neutralized by the B substance contained in the stain and thereby prevented from exerting further action against Group B substances so that when the supernatant was tested against Group B cells, no reaction took place. The anti-A in the liquid, on the other hand, since it met no Group A substance, was not used up and was still active in the supernatant liquid.

The volume of the reagent applied to the stain should permit an excess of two or three loopfuls; the concentration of the reagent should be such that anti-A and anti-B are approximately 1:8 of human serum of 1:64 titer.

During the test of the supernatant, which is usually carried out on a microscope slide, provision must be made to prevent evaporation. This can be done by a moist chamber or a sealed hanging-drop preparation.

The possible reactions are as follows: the stain may remove neither anti-A nor anti-B or may remove one or the other, or both. In each case the diagnosis of the blood group of the stain is shown: Group O, no agglutinin removed; Group A, anti-A removed; Group B, anti-B removed; Group AB, anti-A and anti-B removed.

In order that the highest confidence may be placed on the test it is extremely desirable that at the same time stains of known group and of similar age be tested under similar conditions. When all reagents are suitably chosen, and the tests are properly conducted, stains no larger than 1 sq. cm. in area may be identified. Age alone, in the absence of putrefaction, is not a serious limitation, for evidence has been put forward that stains forty years old have been correctly identified.

Another desirable control is to test the material away from the stain — cloth, paper or whatever it may be — to demonstrate the absence of specific or nonspecific power to remove either anti-A or anti-B agglutinin from the reagent.

It is possible to confirm a grouping by testing a recent stain for the agglutinins anti-A or anti-B, or both. The finding of both in a stain thought to be Group O is a welcome confirmation. These tests are best carried out by the "crusts" technic of Latter. However, the agglutinins deteriorate more rapidly than the agglutinogens.

WILLIAM C. BOYD, PH.D.
Professor of Immunochemistry, Boston University School of Medicine.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SEROLOGIC TESTS FOR VIRUS DISEASES

The Department has previously announced to physicians its facilities for performing a limited number of serologic tests for certain virus diseases, such as influenza A and B, mumps and lymphocytic choriomeningitis. To this list is now added tests for cold agglutinins, useful in the diagnosis of atypical pneumonia, as well as complement-fixation tests for the more common encephalitides.

Specimens should be submitted in the Department's special outfit, and accompanied by properly filled out forms entitled "Request for Serologic Tests for Certain Virus Diseases." The "agglutinations-cultures outfit" to be used (previously called the "undulant-fever outfit") and the special forms to be filled out may be obtained from local boards of health, or directly from the Massachusetts Department of Health, Bacteriological Laboratory, 281 South Street, Jamaica Plain 30.

In each suspected case, two aseptically collected 4-cc. serum specimens are required, the first taken as soon as possible after the onset of the disease, and the second ten to fourteen days later (six weeks or more after onset for neutralization tests in cases of lymphocytic choriomeningitis). If facilities for separation of serum are not available, 10 cc. of clotted blood for each specimen may be substituted if it is mailed to the laboratory at once. *Since positive diagnosis can be made only if a rise in antibody titer is demonstrated (fourfold or greater is considered significant) during the course of the illness, two specimens must be sent.* Tests for diagnosis, therefore, will be run only on paired specimens. If information regarding past *mumps* infection and

consequent immunity alone is desired, however, only one specimen need be submitted.

For information regarding serologic diagnosis of other virus infections, the Laboratory should be consulted directly (telephone, JAmaica 4-5440). It should be noted that none of these tests will assist in confirming diagnosis during the early acute stage. They are useful mainly in making diagnosis in retrospect. Since funds for these services are limited, physicians should send specimens of real diagnostic importance only.

UNUSUAL SEROLOGIC TESTS

It is not practical for a state laboratory to attempt to perform certain unusual tests requested by physicians infrequently and at irregular intervals. It has been the practice to forward such specimens to one of the laboratories of the United States Public Health Service.

Some of the unusual serologic tests formerly performed at the National Institutes of Health, Bethesda, Maryland, are now being done entirely at the Communicable Disease Center in Georgia. These are amebiasis, trichinosis, echinococcus and leptospirosis. These specimens should hereafter be sent to Immunology-Serology Laboratory, Communicable Disease Center, United States Public Health Service, Chamblee, Georgia.

Serologic tests for trypanosomiasis, schistosomiasis, filariasis, leishmaniasis and toxoplasmosis should still be sent to Laboratory of Tropical Diseases, National Institutes of Health, Bethesda 14, Maryland.

DISCONTINUANCE OF DISTRIBUTION OF VARIOUS DRUGS

The Massachusetts Department of Public Health has discontinued the distribution of neoarsphenamine, sulfarsphenamine and sulfathiazole tablets. However, the distribution of Mapharsen and bismuth subsalicylate in oil to private physicians for the treatment of patients with syphilis will be continued.

MISCELLANY

MASSACHUSETTS ASSOCIATION OF SCHOOL PHYSICIANS

At a meeting of the interim committee of the Massachusetts Association of School Physicians, attended by Drs. Mary Moore Beatty, Antonio Milone, Anthony H. Nikiel, Alan Poole, Honoria K. Shine and Allan R. Cunningham, chairman, and held on September 11 at Hotel Sheraton, Worcester, a draft of the proposed constitution was completed.

Copies of this draft will be mailed to each of the 620 school physicians of Massachusetts, and further organization will proceed by meetings of school physicians in each of the eight health districts of the Commonwealth.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Manual of Clinical Laboratory Methods. By Opal E. Helper, Ph.D., M.D., associate professor of pathology, Northwestern University Medical School, director of the clinical laboratories, Montgomery Ward Clinics and Passavant Memorial Hospital, and consultant in clinical pathology, Children's Memorial Hospital, Chicago. With a foreword by James P. Simonds, Ph.D., M.D. Fourth edition. 4°, cloth, 387 pp. with 36 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $8.50.

The first edition of this standard work was published originally in 1935. The soundness and popularity of the manual is attested by the need of this fourth edition. The book is intended primarily for use in the teaching of medical students and laboratory technicians, and is not designed as a textbook on clinical pathology. In most instances only one method is included for each determination, and the procedures are given in outline form so that they may be followed easily in the laboratory. There is a comprehensive index, and the book is well published. It should prove useful to the laboratory worker.

The Psychoanalytic Reader: An anthology of essential papers with critical introductions. Volume I. Edited by Robert Fliess, M.D. 8°, cloth, 392 pp. New York: International Universities Press, Incorporated, 1948. $7.50.

This volume, the first in a projected series, comprises important contributions selected from the literature of the period beginning with 1909 and extending to date. The material is divided into five parts: clinical; theory; miscellaneous; uncollected papers of Karl Abraham; and references by Freud (to six publications of other authors). The part on theory includes the articles on female and preoedipal sexuality. There should have been an index, if only of authors. The series should be in all collections on the subject.

Child Psychiatry. By Leo Kanner, M.D., associate professor of psychiatry, Johns Hopkins University School of Medicine, and director, Children's Psychiatry Service, Johns Hopkins Hospital. With prefaces by John C. Whitehorn, M.D., Henry Phipps Professor of Psychiatry, Johns Hopkins University School of Medicine; Adolf Meyer, M.D., LL.D.; and Edwards A. Park, M.D. Second edition. 4°, cloth, 752 pp. Springfield, Illinois: Charles C Thomas, 1949. $8.50.

This standard work was published first in 1935 and reprinted four times from 1937 to 1947. In this second edition the author has completely rewritten his book, incorporating the great advances made in the subject during the past thirteen years. This second edition was published simultaneously in the United States, Great Britain and Canada, and in Spanish in Chile. The text is divided into four parts: history; basic orientation; clinical considerations; and phenomenology, again subdivided into three sections, including personality problems arising from physical illness, psychosomatic problems and problems of behavior. The material is well arranged and well written and documented throughout with references to the appropriate literature. There are indexes of authors and subjects. The printing is well done with a beautiful, large type. The book is recommended for all medical and sociologic libraries and to psychiatrists and pediatricians.

NOTICES

ANNOUNCEMENT

Dr. Francis X. Walsh announces the removal of his office to 1826 Centre Street, West Roxbury.

LAY MEETING ON DIABETES DETECTION

A lay meeting on diabetes detection will be held in the John Hancock Hall of the new John Hancock Building in Boston on October 10. Sponsoring organizations are the New England Diabetes Association, the Committee on Diabetes of the Massachusetts Medical Society and the American Diabetes Association.

The following outstanding investigators in the field of diabetes will speak: Dr. H. C. Hagedorn, of Copenhagen, Denmark, the discoverer of protamine insulin; Dr. Charles H. Best, winner of the Nobel Medal and co-discoverer of insulin; and Dr. Howard F. Root, of Boston.

Announcement of gifts from Denmark and Canada for the establishment of research foundations in the United States will be made at the meeting.

BOSTON CITY HOSPITAL OFFICERS' ASSOCIATION

The second in a series of Tuesday evening lectures sponsored by the Boston City Hospital House Officers' Association will be held in the New Cheever Amphitheater of the Dowling Building, Boston City Hospital, on Tuesday, October 11, at 7 p.m. Dr. Charles P. Bailey, associate professor of surgery, Hahnemann Medical College, Philadelphia, will speak on the subject "Commisurotomy for Mitral Stenosis." Drs. Laurence B. Ellis, Dwight E. Harken and John W. Strieder will lead the discussion.

All interested persons are invited to attend.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A regular meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, on Tuesday, October 11, at 8 p.m.

Dr. Seymour S. Kety, professor of clinical physiology, University of Pennsylvania School of Medicine, will speak on the subject "Physical and Physiologic Factors Regulating the Uptake of Anesthetic Gases."

NEW ENGLAND VENEREAL DISEASE CONTROL CONFERENCE

The New England Venereal Disease Control Conference will be held in the Gardner Auditorium, State House, Boston, on Wednesday, October 12.

PROGRAM

Morning Session (10:00 a.m. to 12:00 noon):

The Effectiveness of the Multiphase Screen-Testing Program as a Syphilis Case Finding Mechanism.

Funds for Syphilis-Control Activities in the Light of a Consistently Declining Reported Morbidity.

Evaluation of American Venereal-Disease-Control Activities.

Interstate Premarital Regulations and Standard Certificate — A Progress Report.

Promiscuity — A Psychiatric Approach.

Afternoon Session (2:00–4:00 p.m.):

Newer Experimental Treatment Schedules of Syphilis.

The Immobilization Test of *Treponema pallidum* and Practical Application.

The Management of Neurosyphilis.

Nonspecific Urethritis.

The Present-Day Treatment of Syphilis.

MASSACHUSETTS CHAPTER, AMERICAN ACADE OF GENERAL PRACTICE

The annual meeting and fall clinical program of the Ma sachusetts Chapter of American Academy of General Practi will be held in Boston on October 19. The morning progra will be held at the Massachusetts General Hospital, wi medical and surgical clinics by the staff of the hospital. Th luncheon, afternoon lecture program and banquet will b held at Hotel Puritan. Mr. Mac F. Cahal, executive secr tary of the American Academy of General Practice, Kans City, will be the speaker.

CONFERENCE OF PROFESSORS OF PREVENTIVE MEDICINE

The annual meeting of the Conference of Professors Preventive Medicine will be held in New York City October 24. Luncheon and afternoon sessions will be held Parlor 1, Hotel Statler. Dr. David D. Rutstein, of Bosto is secretary.

PEDIATRIC SEMINAR FOR PHYSICIANS AND GENERAL PRACTITIONERS

A pediatric seminar for pediatricians and general pra titioners will be held on November 23 and thereafter ever second and fourth Wednesday of the month at 7 p.m. Amphitheater 3A of the White Building, Massachuset General Hospital, by the staff of the Children's Medic Service, Burnham Memorial Hospital for Children, Ma sachusetts General Hospital.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

OCTOBER 7. Veterans Administration Course in Clinical Electrocardiography. Page 510, issue of September 29.

OCTOBER 10. Lay Meeting on Diabetes Detection. Notice above.

OCTOBER 10–21. New York Academy of Medicine. Page 510, issue of September 29.

OCTOBER 11. Boston City Hospital House Officers' Association. Notice above.

OCTOBER 11. New England Society of Anesthesiologists. Notice above.

OCTOBER 11–15. American Society of Clinical Pathologists. Drake Hotel, Chicago.

OCTOBER 12. New England Venereal Disease Control Conference. Notice above.

OCTOBER 13. Mononucleosis. Dr. Andrew Contratto. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

OCTOBER 14. Tuberculosis Rehabilitation Society. Page 434, issue of September 15.

OCTOBER 19. Massachusetts Chapter, American Academy of General Practice. Notice above.

OCTOBER 24. Conference of Professors of Preventive Medicine. Notice above.

OCTOBER 24–26. National Gastroenterological Association. Page 251, issue of August 11.

OCTOBER 24–28. American Public Health Association. Page 251, issue of August 11.

OCTOBER 28. Massachusetts Psychiatric Society. Page 434, issue of September 15.

NOVEMBER 2. New England Obstetrical and Gynecological Society, Hotel Somerset, Boston.

NOVEMBER 2–5. Pan-American Congress of Pediatrics. Page 251, issue of August 11.

NOVEMBER 3–5. American Association of Blood Banks. Page xi, issue of June 16.

NOVEMBER 7–9. National Society for Crippled Children and Adults. Page 184, issue of July 28.

(*Notices concluded on page xi*)

To a patient with troubles internal
That seemed to be centered substernal,
Said our friend, Dr. Wise, "I must digitalize,
***After checking the ads in the* Journal."**

4